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13. SUPPLEMENTARY NOTES

14. ABSTRACT: NACTN is a clinical trials network that tests promising therapies for spinal cord injury (SCI) and maintains a patient registry that as of 5/12/15 has extensive data on 762 acutely injured patients; this is an ongoing study at all clinical centers. Registry data is available to non-NACTN scientists to facilitate the design of clinical trials. NACTN successfully conducted a Phase 1 safety study of the neuroprotective drug riluzole (*Journal of Neurotrauma* 31:239-255 (February 1, 2014) and in partnership with AOSpine North America (AOSNA) is participating in an international multi-center Phase 2/3 study to test the efficacy of riluzole in acute SCI. NACTN centers will conduct a pharmacology substudy within the Phase 2/3 trial that monitors changes in the drug's metabolism after SCI and correlates pharmacokinetics with outcome measures. NACTN is finalizing the DOD and local IRB regulatory requirements and anticipates that its sites will be fully engaged in the RISCIS and PK studies by year-end. The Riluzole in Acute Spinal Cord Injury Study (RISCIS): Rationale, Design and Critical Endpoints" has been accepted for publication in the journal *Spinal Cord*. A NACTN/AOSNA supplement to the *Journal of Neurosurgery: Spine*, v17 was published September 1, 2012 in print and online (http://thejns.org/toc/spisup/17/1); the papers are based primarily on the Riluzole Phase 1 study and NACTN's SCI registry data.

15. SUBJECT TERMS Spinal Cord Injury (SCI), North American Clinical Trials Network (NACTN), International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (formerly American Spinal Injury Association scores), riluzole, RISCIS, neuroprotection, pharmacokinetics, pharmacodynamics, efficacy, AOSpine North America (AOSNA), Contract Research Organization (CRO)

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1. Introduction

NACTN's mission is to carry out clinical trials of the comparative effectiveness of new therapies for spinal cord injury using an established consortium of neurosurgery departments at university-affiliated medical center hospitals with medical, nursing and rehabilitation personnel who are skilled in the evaluation and management of SCI. There are presently nine clinical sites, including Walter Reed National Military Medical Center (WRNMMC) and Brooke Army Medical Center (BAMC). There are also clinical coordinating, data management and pharmacology centers. The U.S. Army Medical Research and Materiel Command of the Department of Defense (DOD) has supported NACTN since 2006 via contracts W81XWH-07-1-0361, W81XWH-10-2-0042 and the current active award, W81XWH-13-2-0040. On April 22, 2015, Reeve's one-year No Cost Extension request was approved, thereby extending the Period of Performance on this award until April 30, 2016. NACTN has successfully completed a Phase 1 study of the neuroprotective drug riluzole and is participating in a Phase 2/3 clinical trial in collaboration with AOSpine North America (AOSNA). Additionally, the network continues to enroll acutely injured spinal cord patients into its data registry, analyze the data, share it with other clinical and academic investigators, and engage with industry and academic groups interested in testing potential therapies in rigorous clinical trials.

2. Keywords

Spinal Cord Injury (SCI), North American Clinical Trials Network (NACTN), International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (formerly American Spinal Injury Association scores), riluzole, RISCIS, neuroprotection, pharmacokinetics, pharmacodynamics, efficacy, AOSpine North America (AOSNA), Contract Research Organization (CRO)

3. Accomplishments

Major Goals

1. Continued planning and implementation of an acute spinal cord injury Phase 2/3 clinical trial of the neuroprotective drug riluzole.
2. Continued enrollment of acutely injured subjects into the data registry.
3. Ongoing assessment of other potential therapeutics to be tested.
4. Continued analysis of data for publications and presentations.
5. Strengthening NACTN's leadership and guidance among the international companies, agencies, NGOs and other entities that are grappling with the enormous challenges of prioritizing appropriate therapies to be tested in human trials, organizing the studies and raising the money to fund them.

The goal of the RISCIS Phase 2/3 clinical trial is to develop a neuroprotective therapy for SCI that can be administered enterally at frontline medical care stations shortly after injury. Specifically the hypothesis being tested is that riluzole administered within 12 hours of an acute traumatic spinal cord injury will improve the outcome of patients with a cervical SCI with the greatest efficiencies being in ISNCSCI AIS grade B and C patients.

Under the RISCIS umbrella, NACTN centers will conduct a pharmacology substudy that monitors changes in the drug's metabolism after SCI and correlates pharmacokinetics with outcome measures. Here the hypothesis is that a therapeutic level of plasma concentration of riluzole can be established, thus building upon the pharmacological study initiated in the Phase 1 trial, results of which have now been published (Grossman et al, *Journal of Neurotrauma* 31:239–255 February 1, 2014) (Appendix A).

Lastly, continued enrollment of acutely injured patients into the NACTN data registry to track over time their natural course of recovery and outcomes, complications and other events expands upon the registry as a unique resource for the field. The data can be used as a "prior group" for comparative purposes in clinical trials, as it was used in the riluzole Phase 1 study.

NACTN made tangible advancements on all of the major goals of this award during the research period May 1, 2014 – April 30, 2015:

RISCIS

The universities of Maryland, Toronto and Virginia and Thomas Jefferson University are designed AOSpine/NACTN sites and are funded by AOSNA for the RISCIS study; they will be funded by Reeve for the PK substudy. At this time, all four are enrolling in RISCIS.

The universities of Louisville, Miami, UT Houston and BAMC are designated NACTN sites and will be funded by Reeve for both RISCIS and the PK substudy. None of these sites have yet begun RISCIS enrollment. The PK substudy has not yet begun at any NACTN site pending final DOD and IRB regulatory approvals.

Walter Read National Military Medical Center is not participating in RISCIS because it does not treat acutely injured patients.

The status of NACTN in RISCIS is as follows:

1) The RISCIS master protocol was amended with the required DOD language as was the PK protocol
2) RISCIS completed preliminary review by TATRC's regulatory compliance specialist Jill Ciccarello and on July 27, 2014 and her recommended changes to the documents were made in collaboration with the RISCIS Contract Research Organization (CRO), Nor-Consult, LLC. The revised protocol was submitted for expedited review to Houston Methodist Hospital Research Institute's IRB; approval was given on September 2, 2014.
3) In September 2014, the Reeve Foundation and the CRO finalized the RISCIS site agreement, the legal document that governs the roles and responsibilities of all parties (Reeve, NACTN sites and AOSpine North America) in the Phase 2/3 clinical trial.
4) Immediately thereafter, the CRO began negotiations with NACTN's clinical centers on the Non-Disclosure (NDA) and Clinical Trial Agreements (CTA) and the PK substudy Amendment. As of this report date, BAMC's regulatory pathway is complicated by the PI's (Joseph Hobbs, MD) pending deployment in early fall and the need to add a co-PI as a result; Louisville's Clinical Trial Agreement remains under legal review. All other sites clinical centers have fully executed NDAs, CTAs and PK Amendments.
5) Brian Garland, Protocol Coordinator with the USAMRMC Office of Research Protections, Human Research Protection Office (HRPO), completed an initial triage/review of the project and Elizabeth Toups, NACTN Project Manager, submitted it to Suzanne Dolney, DOD, HRPO, ORP, USAMRMC, for approval in October 2014.
6) The Methodist approved protocol and supporting documents were distributed to each participating NACTN sites on September 10, 2014 for local IRB approval.
7) On October 28, 2014, Suzanne, HRPO, requested a "temporary submission hold" on sites submitting to their local IRBs until possible minor changes to the RISCIS DOD addendum and ICFs could be made. Those modifications were received on November 24, 2014 and the amendment was submitted to Methodist IRB on December 2, 2014; approval was received on December 30, 2014.
8) Methodist's approved amendment was distributed to NACTN clinical centers for local IRB approval on January 5, 2015; at this writing the University of Virginia has received local IRB approval; it along with the Human Research Protocol Submission Form for Headquarters Level Administrative Review of Extramural Research, was submitted on May 5, 2015 to US Army Medical Research and Material Command Office of Research Protections. Thomas Jefferson University has also received local IRB approval and NACTN's Coordinating Center is preparing the Human Research Protocol Submission Form and related documents for final review and regulatory approval by DOD. NACTN and the RISCIS CRO are working closely with the remaining NACTN sites to expedite their regulatory reviews in every way possible.

9) Since the December 2014 start of the RISCIS trial, several new sites have been on boarded: Sunnybrook and St. Michael's hospitals in Toronto and Prince of Wales and Royal North Shore hospitals in Sydney, Australia. Royal Adelaide Hospital will soon be joining as the third Australian site. Finally, Michael Fehlings, MD, PhD is in discussion with potential sites at Charite Hospital in Berlin and at Cambridge University.
10) A second substudy, funded by the Canadian Rick Hansen Institute (RHI), "Development of MRI-based Biomarkers in Patients with Acute Spinal Cord Injury", is underway and seeks to determine if certain MRI techniques are able to capture information that reflects the severity of the injury and indicates a more accurate prognosis.
11) The first RISCIS Steering Committee conference call was held on April 13th; members include the RISCIS PI (Fehlings) and co-PI (Grossman), NACTN Project Manager (Toups) and representatives from the funding agencies (Reeve, AOS, RHI, Ontario Neurotrauma Foundation). The agenda focused on the trial update and notable successes to-date and/or challenges.
12) As of May 20, 2015, 20 subjects have been enrolled in the trial.
13) On April 29-30, Elizabeth Toups (Project Manager) and Jerika Acosta (NACTN Site Monitor) attended a study protocol training session with the CRO, Nor-Consult, in Seattle, Washington.

NACTN SCI Registry

The NACTN SCI Registry, a core function of the North American Clinical Trials Network (NACTN), serves two vital purposes. The first is to provide a statistical and scientific platform to develop the data, logistics and collaborations necessary to conduct Phase I and Phase II clinical trials of emerging neuroprotective and neuroregenerative therapies, particularly those that can be administered in the very early stages of injury. A second and equally important purpose is to develop high quality, standardized, and validated acute care and follow-up data on a representative national sample of male and female adult patients who have suffered a traumatic spinal cord injury with neurological deficits. This acute care and follow-up data are an invaluable and unique resource needed to characterize the trajectory (natural history) of individuals who have suffered a spinal cord injury.

All data are collected prospectively starting at the time of admission to a NACTN clinical center. The registry data includes extensive demographic information, past medical history, pre-injury medication use, circumstances of injury, time of injury, and the time of arrival to the treating NACTN hospital. Further detail is elicited about the condition of the patient on arrival and includes a clinical evaluation, measurement of state of consciousness with the Glasgow Coma Scale (GCS) and of associated injuries with the Abbreviated Injury Scale. The American Spinal Injury Association impairment scale (AIS) is scored on admission and at key times throughout the patients' hospital and post-hospital course. All examiners received training on performing the AIS examination and study procedures. Data are also collected on radiographic findings, non-operative and operative treatments, timing of treatments, and perioperative complications. Discharge AIS score, and the type of facility to which the patient was transferred are recorded in the discharge form. After acute care discharge, Long-term follow-up is scheduled at approximate intervals of six and twelve months after discharge. The follow-up registry protocol includes: the AIS Impairment Scale, and where appropriate, the Functional Independence Measure FIM™, the Spinal Cord Independence Measure (SCIM), and the Walking Index for Spinal Cord Injury (WISCI) evaluations.

Currently there are nine clinical centers participating in the registry and as of 05/12/2015, 762 patients have been enrolled into the NACTN SCI Registry. Stanford University has just now begun to screen patients for enrollment.

Tables in Appendix B provide a profile of SCI cases currently in the registry database. As of 05/12/2015, clinical coordinators at the NACTN clinical sites have screened 1387 SCI patients for registry eligibility. Informed Consent to record prospective standardized acute care treatment data and follow-up data for up to one-year after acute care discharge was given by 762 patients (Table 1). Of these, acute care treatment records for 698 patients are currently in the registry research database with an additional 64 patient records pending entry

into the electronic data entry system. The following text summarizes selected demographic, treatment, and outcome information for 687 patients with complete inpatient discharge data.

The majority of registry cases are male (80%) and white (69%).The median age at injury is 43 years; approximately 78% of the 687 registry cases are 20 to 65 years-of-age and 17% are older than 65 (Table 2).

Table 3 lists the circumstances of SCI injuries. The leading circumstances of injury were falls (36%) and motor vehicle accidents (31%). Recreation including sports injuries accounted for (10%). Diving was responsible for 63% of all recreation injuries. Civilian assaults accounted for 44 cases (6%) of all SCI injuries.

Military personnel accounted for 16 (2%) of all SCI injuries. Of these, 15 were SCI injuries transferred from Landstuhl (Germany) Regional Medical Center to Walter Reed Army Medical Center (WRAMC). Five of these 15 cases were penetrating bullet wound injuries; seven were classified as blast (IED) injuries; 1 the result of a helicopter crash, and 1 due to an accidental fall. Fourteen Landstuhl cases were transferred to WRAMC within 2 to 9 days of injury and one case transferred 18 days after injury. The lone stateside military case transferred to WRAMC was a SCI injury due to a surfing accident, and this case was transferred to WRAMC 15 days after injury from a civilian hospital in Virginia Beach, VA.

Approximately 57% of civilian SCI patients arrived by EMS directly from the site of injury to a NACTN center with a median arrival time of approximately 1 hour. Of patients transferred from intermediate hospitals the median arrival time post-injury at a NACTN center was 9 hours.

The distribution of AIS severity of patients with a first AIS within 7 days of injury is given in Table 4; AIS A (33%), AIS B (10%), AIS C (13%), AIS D (24%), AIS E (6%). Approximately 15% of the 647 patients did not have initial AIS recorded within 7 days of injury.

Of the 687 cases, 36% had no reported complications or intercurrent events during acute care whereas 65% had at least one mild, moderate or severe complication (Table 5). Of the total number of complications ascertained during acute care (1,774) and reported in Table 6, pulmonary, infections, cardiac, and hematologic complications accounted for 75% of all complications. Table 6 also reports the number of patients accounting for each type of complication. For example, 210 patients experienced 410 pulmonary complications giving an incidence rate of 210/687 (30.6%) for pulmonary complications. Incidence rates for each type of complication are given in the last column of Table 6.

The vast majority of SCI injuries were blunt injuries (80%) or crushing injuries (13%), but 5% were penetrating SCI injuries, primarily bullet injuries. Of the 670 patients, 73% sustained cervical injuries and 20% thoracic injuries (Table 7).

Surgical and corticosteroid treatments are summarized in Tables 8 and 9. Of patients evaluated as AIS A through AIS D within 7 days of injury 92% were surgically treated whereas 62% of AIS E patients were surgically treated. Approximately 47% of AIS A through AIS D patients received corticosteroid treatment. The distribution of steroid use by first AIS grade is given in Table 9.

Length of acute care hospitalization and discharge status is summarized in Table 10. For 687 SCI patients, approximately 47% had a length of hospital stay exceeding two weeks. Nearly three quarters of the SCI patients were discharged to a rehabilitation hospital (73%) and nearly 6% were transitioned to either long-term acute care or a nursing home. Rehabilitation was initiated for 84% of the patients prior to discharge from acute care.

Table 11 contrasts the AIS grades at admission to AIS grades at hospital discharge for 511 SCI patients for whom complete data is currently available. Notable is that 88% of patients with a grade of AIS A at admission remained AIS A at discharge. Although there was improvement within each AIS grade, the improvement in AIS

A through AIS C patients at the time of acute care discharge was modest. Table 12 compares AIS grades at admission to AIS grades at 6-months post-injury for 285 patients. Substantial improvement in outcomes at 6 months was seen at all AIS grades.

In summary, important milestones have been achieved with the registry. Enrollment of 762 participants has demonstrated that is feasible to acquire prospective standardized research quality clinical data on traumatic SCI patients. Registry data has enabled a much more precise and nuanced understanding of the natural course of recovery after injury and the data has been disseminated across the scientific and medical communities through numerous NACTN publications and presentations. Additionally non-NACTN investigators are making use of the registry to further their own research and clinical studies. All policies and processes related to data-sharing initiatives are codified in the NACTN Governance manual. Finally the recent transition from paper-submission of data to an electronic data capture system has meant that error and data integrity checking can be done in a more timely fashion, if not almost instantaneously, a vast improvement over the more tedious checking done during the paper submission era.

InVivo Therapeutics is in the process of requesting access to NACTN's registry data to be used as a control for the company's planned Phase 2 pivotal clinical trial. A Phase 1 study (five patients) is now underway looking at the safety of the InVivo neuro-spinal scaffold, a polymer designed to help the spine heal, and then degrade in the body. Preclinical contusion model data shows that the scaffold maintains white matter tracts, reduces cyst formation, and causes an influx of cells into the site of injury (those cells are being characterized now). NACTN has established an external data dissemination policy to be followed by any individual or company requesting use of SCI Registry data (Appendix C).

Assessment of Potential Therapeutics

Lead by Charles Tator, MD, PhD, chairman of NACTN's Therapy Treatment Selection Committee, investigators keep abreast of promising interventions that emerge from the R&D pipeline; this sometimes includes discussions with industry representatives who reach out to NACTN as a resource for their clinical trial planning and implementation.

Susan Howley, Reeve's Executive Vice President, Research, met with Dr. Stephen Huhn, on November 18, 2014 in New York City to discuss StemCells, Inc.'s Pathway® Study, a Phase II proof of concept clinical trial to explore the safety and efficacy of the company's human neural stem cells for the treatment of cervical spinal cord injury. The study is a randomized, controlled, single-blind study and efficacy will be primarily measured by assessing motor function according to the International Standards for Neurological Classification of Spinal Cord Injury. The primary efficacy outcome will be change in upper extremity strength as measured in the hands, arms and shoulders. Trial subjects will be followed for one year post-transplant. Presently, XXX NACTN sites are enrolling subjects; Maryland and Miami are actively recruiting subjects; Thomas Jefferson University, UT Houston, Toronto and Stanford are poised to enter the trial soon. No DOD funding is being used for the NACTN sites engaged in the Pathway® Study but NACTN PIs worked closely with the company on the study design.

In March, NACTN was approached by RhinoCyte, Inc. (Louisville, KY) about participating in their planned "Innovative Phase I Program" designed to treat 20 severely injured spinal cord patients with RhinoCyte's 4Q2015 (adult stem cells from the rhino-epithelium. Following careful review of the technology, Drs. Tator and Grossman advised the company that its involvement in RISCIS precluded trial participation but they did offer to provide assistance with the protocol design.

Data Analysis for Publications/Presentations

A specific aim of Reeve's initial DOD award, W81XWH-07-1-0361, was to characterize the biomechanical, anatomical and neurological differences between military and civilian injuries and differences in their outcomes. WRNMMC undertook this retrospective study under the leadership of NACTN Principal Investigator Michael K. Rosner, MD, COL, MC, USA, who will submit the manuscript, Spine Injuries

Sustained by US Military Personnel in Combat Are Different From Non-Combat Related Spine Injuries, Nicholas S. Szuflita, Chris J. Neal, Michael K. Rosner, MD, Ralph F. Frankowski, Robert G. Grossman, to *Military Medicine* for review. (Appendix D)

The paper Rationale, design and critical endpoints for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): A randomized, double-blinded, placebo-controlled parallel multi-center trial, MG Fehlings, H Nakashima, N Nagosh, DSL Chow, RG Grossman, B Kopjar, has just been published in the journal *Spinal Cord* (2015), 1-8 1362-4393/15 (Appendix E)

NACTN investigators met on May 3, 2015 at the AANS meeting in Washington DC to discuss the status of the RISCIS regulatory process (DOD and local IRB) for NACTN clinical centers, patient enrollment in RISCIS, and a webinar/conference call to develop protocols for using the NACTN data registry to answer questions of clinical importance. It was agreed that a priority will be the study of the long-term outcome of patients with a central cord injury. Of particular interest are factors predisposing to injury, presence of myelopathy prior to the acute injury, timing of surgery, type of surgery, and long-term outcome. The June 17th NACTN PI conference call will be dedicated to finalizing the research questions to be asked and the committees to work on each.

Leadership

There has been a recent uptick in inquiries to NACTN from academic and biotechnology entities exploring and/or planning for spinal cord injury clinical trials and outreach from academic research institutions inquiring about NACTN membership. Presently Reeve cannot consider any expansion that would involve added financial expense – the current DOD award (#0042) and the pending contract (JWMRP 2014) have no budgeted allowance for expansion. Nevertheless there are sites motivated to join NACTN in spite of the lack of funds and they opt to do so as a self-fund center. On November 3, a Letter of Agreement from the Christopher Reeve Foundation was submitted to Louisiana State University Health Sciences Center – New Orleans. Dr. Jason Wilson, MD, MS, Associate Program Director will serve as the NACTN PI. The Department of Neurosurgery received 178 SCI patients in their ED at the LSU Hospital Level 1 Trauma Center in 2013. We believe LSU will make an important contribution to the NACTN SCI Registry**.** Precise details of the membership are still being discussed.

What opportunities for training and professional development has the project provided? Since its inception, NACTN has afforded a myriad of opportunities for its members to broaden and enrich skills and expertise, where through specific training efforts or network interaction with other scientists and clinicians. The network's study coordinators and PIs have participated in training to standardize patient assessments and data collection across all sites. On occasion an outside expert has provided input on, for example, Bayesian statistical analysis and the PIs have attended non-NACTN spinal cord meetings and presented NACTN's research. The investigators participated in the trial design discussions for the riluzole Phase 1 and RISCIS Phase 2/3 studies and they have been invited to contribute input to the planning for and the design of other trials by academics, biotech and big pharma. Following all regulatory approvals, NACTN clinical personnel will be trained by the RISCIS CRO on all aspects of the study: patient enrollment, drug delivery and data collection and reporting and the like.

How were the results disseminated to communities of interest? Communities of interest for Reeve and NACTN include but are not necessarily limited to scientific, medical and patient. NACTN investigators disseminate their findings through publications, presentations (posters, lectures, symposia) at a myriad of meetings and by interacting with others planning spinal cord clinical trials, including making data from NACTN's patient registry available. Examples of publications include: *Journal of Neurosurgery* 2013 Jul 16. [Epub ahead of print], A Prospective Multicenter Phase 1 Matched Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury, Grossman RG, Fehlings M, Frankowski R, Burau KD, Chow D, Tator C, Teng Y, Toups EG, Harrop JS, Aarabi B, Shaffrey C, Johnson MM, Harkema S, Boakye M, Guest J, Wilson JR; A NACTN/AOSNA Focus Issue on Spinal Cord Injury, supplement to the *Journal of Neurosurgery: Spine*, Volume 17, was published September 1, 2012, in print and

online at (http://thejns.org/toc/spisup/17/1). The 17 papers are primarily based on the Riluzole Phase 1 study and on NACTN registry data; and most recently, Rationale, Design and Critical Endpoints for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): A randomized, double-blinded, placebo-controlled parallel multicenter trial, Michael G. Fehlings, MD, PhD, FRCS, FACS, Hiroaki Nakashima MD, Narihito Nagoshi MD, PhD, Diana S. L. Chow, PhD, Robert G. Grossman, MD, Branko Kopjar, MD, MS, PhD (accepted for publication in *Spinal Cord*), and Spine Injuries Sustained by US Military Personnel in Combat Are Different From Non-Combat Related Spine Injuries, Nicholas S. Szuflita, Chris J. Neal, Michael K. Rosner, MD, Ralph F. Frankowski, Robert G. Grossman (being submitted to *Military Medicine*).

The Reeve Foundation periodically updates the patient community on NACTN activities through its research blog (www. http://www.spinalcordinjury-paralysis.org/blogs/18) and in its print newsletters.

Plans to accomplish the major goals of this award: As all regulatory requirements are met by each NACTN clinical center, RISCIS enrollment will begin and the DOD-funded pharmacology substudy intended to obtain information about pharmacokinetics and pharmacodynamics of riluzole and relate that information to toxicity and efficacy outcomes will commence. NACTN will contribute to RISCIS data analysis and subsequent publications and will do all of the PK substudy data analysis and manuscript writing.

NACTN will continue to enroll acutely injured patients into its data registry; the PIs are preparing to initiate data analysis designed to answer a series of specific research questions they are posing. Manuscripts will be prepared and submitted for review and publication – potentially an important contribution to the spinal cord field.

Both at the network and individual investigator levels, NACTN is expanding its influence and leadership in the field. Academics and industry alike seek counsel and participation in their studies, and Reeve and NACTN leadership align with other NGOs as appropriate to advance the shared mission of translating promising therapies from bench to bedside.

4. Impact

What was the impact on the development of the principal discipline(s) of the project? NACTN has had a demonstrable impact on the spinal cord field. First, its riluzole Phase 1 study was carefully designed and the promising results were shared with the field via publication. This was a step forward because so many earlier pharmaceutical trials had failed for a variety of reasons; these failures informed how NACTN designed and implemented its Phase 1 study. We believe the Phase 1 pharmacology study raised the bar in the field and that combined with results of the RISCIS PK substudy, we should be able to more precisely calibrate dosing for optimum outcome. For a patient population with grave unmet needs (there are no proven safe and effective acute treatments, only standard of care), riluzole could prove an important first.

The NACTN data registry has contributed to our understanding of the natural course of recovery from acute traumatic spinal cord injury and in that way is a unique resource for the field; nothing else like it exists. Furthermore, registry data have been used as controls in NACTN's riluzole Phase 1 and discussions are underway with InVivo Therapeutics; with Drs. Francis Farhadi and Russell Lonser at Ohio State concerning NACTN database of complications; and with Dr. John Steeves (University of Vancouver) on a collaboration with NACTN on statistical analysis of SCI trial endpoints for a Canadian Health Network proposal entitled "Enrollment of trial participants and determination of clinical endpoints".

Alan Levi, MD at the University of Miami is comparing a group of acute cervical AIS A SCI patients enrolled and treated at Jackson Memorial Hospital using a University of Miami approved hypothermia protocol to age and injury and other factors matching controls from the NACTN SCI registry.

What was the impact on other disciplines? Nothing to report.

What was the impact on technology transfer? Nothing to report.

What was the impact on society beyond science and technology? If RISCIS successfully demonstrates the continued safety and efficacy of the use of riluzole in acute spinal cord injury, we anticipate there will be a demonstrable impact on the U.S. military and society at large because preserving function will reduce the high economic impact of SCI. Estimated average lifetime costs of health care and living (directly tied to injury) vary across patients and are determined by injury severity. In 2013 dollars, patients at the C1-C4 levels will have yearly expenses of $1,048,259 (first year) and $182,033 each year thereafter. For those at the C 5-C8 levels, those costs are estimated to be $757,459 and $111,669; and for paraplegics (AIS A, B or C), the respective costs are $510,883 and $67,677. These figures do not include estimated lost wages, benefits or productivity (*Spinal Cord Injury: Facts and Figures at a Glance*, August 2014, The National SCI Statistical Center, University of Alabama, Birmingham). Against the backdrop of escalating healthcare costs and reform, any reduction in spinal cord injury expenses is an important one.

5. Changes/Problems

Changes in approach and reasons for change. Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them. In earlier quarterly reports, we have advised concern about the time-consuming nature of the regulatory processes involved in this multi-site trial. That concern has been borne out, as per the ***RISCIS*** section above. Although most sites are close to having DOD and local IRB approvals for both RISCIS and the PK substudy (the exception is BAMC) it has taken almost a full year. At BAMC, the non-disclosure agreement was signed months ago but as of this writing, the Clinical Trial Agreement and the Amendment to the Clinical Trial Agreement (for the PK substudy) remain unreviewed and unsigned. And as reported above at ***RISCIS*** 4, it appears Dr. Hobbs will be deployed in October of this year, necessitating appointment of a co-PI and further slowing regulatory approval.

A second concern previously cited is our anticipation that it will be challenging to enroll the number of patients needed to obtain unequivocal evidence of efficacy of riluzole within the timeframe of the RISCIS study. We anticipate that having all NACTN sites actively consenting subjects into the study will increase and have a favorable impact on the enrollment numbers. The sponsor continues to seek out qualified sites, adding two in Australia in late 2014 and a third, Royal Adelaide Hospital, preparing to open for enrollment shortly; discussions continue with another two potential sites in Europe.

Changes that had a significant impact on expenditures. Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents. Nothing to report.

6. Products

Journal Publications.

Rationale, design and critical endpoints for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): A randomized, double-blinded, placebo-controlled parallel multi-center trial, MG Fehlings, H Nakashima, N Nagosh, DSL Chow, RG Grossman, B Kopjar, has just been published in the journal *Spinal Cord* (2015), 1-8 1362-4393/15 I (federal support is acknowledged)

Spine Injuries Sustained by US Military Personnel in Combat Are Different From Non-Combat Related Spine Injuries, Nicholas S. Szuflita, Chris J. Neal, Michael K. Rosner, MD, Ralph F. Frankowski, Robert G. Grossman (being submitted to *Military Medicine*)

Presentation.

Efficacy & Safety of Riluzole in Acute Spinal Cord Injury (SCI). Rationale & Design of AOSpine Phase III Multicenter Double Blinded Randomized Trial, Fehlings, Michael, Kopjar, Branko, Grossman, Robert, ISCoS and ISNCSCI Joint Scientific Meeting, May 14-16, 2015, Montreal, Canada (Appendix F)

Website.
http://www.christopherreeve.org/site/c.ddJFKRNoFiG/b.8720879/k.B691/NACTN.htm - NACTN is featured in the research section of the Christopher & Dana Reeve Foundation's website. The target audience is the lay reader and more specifically, people living with spinal cord injury, their families and caregivers.

Other Products.
NACTN SCI Registry. A database of the natural history of patients with SCI. As of May 12, 2015, 762 patients were enrolled, which has enabled development of high-quality, standardized, and validated acute care and follow-up data on a representative national sample of adult male and female patients who have suffered an SCI with neurological deficits. These acute care and follow-up data are a unique resource needed to characterize the trajectory (natural history) of individuals who have suffered an SCI. All data are prospectively collected starting at the time of admission to an NACTN clinical center. The Registry data include extensive demographic information, medical history, pre-injury medication use, circumstances of injury, time of injury, and the time of arrival to the treating NACTN hospital. On admission further details are elicited about the patient's condition, including state of consciousness and associated injuries. The ISNCSCI Impairment Scale is scored on admission and at key times throughout the hospital and post-hospital course. Data on radiographic findings, non-operative and operative treatments and their timing and perioperative complications are also collected, as are the discharge ISNCSCI score and the kind of facility to which the patient is transferred. Six and twelve-month follow-up data include the ISNCSCI and other appropriate evaluations.

NACTN SCI Registry data is available to others in the scientific and medical communities to facilitate their research and clinical translation efforts.

7. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Name:	Robert G. Grossman, MD
Project Role:	Principal Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to Project:	Dr. Grossman has oversight of NACTN's scientific and medical activities and is responsible for ensuring the network fulfills its goals as stipulated in the current award's Statement of Work
Funding Support:	90% effort covered from other revenue sources
Name:	Susan Howley
Project Role:	NACTN Administrative Manager and Reeve Point of Contract with DOD
Researcher Identifier:	
Nearest person month worked:	2
Contribution to Project:	Ms. Howley, Reeve Foundation's EVP Research, provides organizational and administrative support to Dr. Grossman, Ms. Toups and NACTN personnel; she is the Reeve/NACTN administrative interface with DOD
Funding Support:	72% effort covered from other federal/private sources

Name:	Elizabeth Toups, MS, MSN, RN
Project Role:	NACTN Project Manager and Point of Contract for DOD HRPO ORP
Researcher Identifier:	
Nearest person month worked	3
Contribution to Project:	Oversees DOD/IRB regulatory activities and NACTN study coordinators; facilitates communication/ collaboration among NACTN sites; involved in every aspect of NACTN programmatic activities
Funding Support	65% effort covered from other revenue sources

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? Nothing to report.

What other organizations were involved as partners?
Historically the most productive partnership has been that between the Reeve Foundation/NACTN and AOSpine North America. AOSNA is a registered, not-for profit 501(c) (3) foundation which is focused on research and education related to spinal conditions. It is based in Paoli, Pennsylvania and is part of the AO Foundation headquartered in Davos, Switzerland.

Our first collaborative effort was publication in September 2012 of the NACTN/AOSNA supplement to the *Journal of Neurosurgery: Spine*, v17, which was published September 1, 2012 in print and online at (http://thejns.org/toc/spisup/17/1); the papers are based primarily on the Riluzole Phase 1 study and NACTN's registry data. In addition to intellectual collaboration, AOSNA contributed financial resources to the conceptual development, writing and publication of this focus issue.

The second active NACTN/AOSNA collaboration is RISCIS, the Phase 2/3 safety and efficacy study of the acute injury drug riluzole. AOSNA, the study sponsor, brings a strong clinical research network to the partnership with NACTN and an in-house CRO (Nor-Consult), which has considerable expertise in running multi-center trials, including the recent experience of examining Riluzole in non-traumatic spinal cord injury (CSM Protect Study). AOSNA has committed more than $3 million in actual and in-kind support, complementing the intellectual, organizational and financial contributions of NACTN to the trial. Drs. Grossman and Michael Fehlings (NACTN PI, Toronto) are the co-PIs of the RISCIS clinical trial.

Other important partnerships for NACTN are those with AOSpine International (data sharing agreement and RISCIS), the Ontario Neurotrauma Foundation (RISCIS) and the Rick Hansen Foundation (funding a RISCIS Magnetic Resonance Imaging substudy). The last two collaborators are Canadian not-for-profit organizations. AOSpine International is headquartered in Duebendorf, Switzerland

8. Special Reporting Requirements

Quad Chart

"North American Clinical Trials Network/ Building Infrastructure to Accelerate Transfer of Basic Research in Spinal Cord Injury (SCI) to Clinical Practice"

W81XWH-13-2-0040 Y2 Q4 QC May 2015

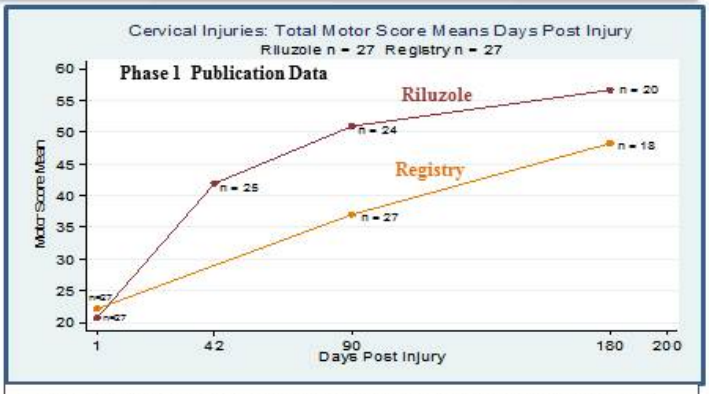
PI: Robert G. Grossman, MD **Org:** Christopher Reeve Foundation **Award Amount:** $2,000,000.00

Study/Product Aim(s)

- Conduct a phase 2/3 clinical trial of the pharmacokinetics, safety & efficacy of Riluzole in acute SCI, in partnership with AOSNA North America
- Continue enrollment of acutely injured patients into the NACTN SCI Registry (762 enrolled to date)
- Assessment of therapies for trials including epidural stimulation & cell transplantation
- Continue analysis of data for publications and presentations
- Continue NACTN's leadership in the SCI field
- Continue dialogue with StemCells Inc. for some NACTN sites to participate in their Phase II Pathway® Study.

Approach

A Phase 2/3 protocol developed by NACTN PIs and experts in clinical trial design will be used for the clinical trial. NACTN SCI Registry data will be used to develop algorithms for predicting outcome after SCI. Analysis of data from the Phase 2/3 clinical trial and SCI Registry for presentations and publications.



Accomplishments: two riluzole publications in ***Journal of Neurotrauma*** *31*:239-255 February 1 2014; ***Spinal Cord*** May 1-8 1362-4393/15
762 patients enrolled in NACTN SCI data registry

Timeline and Cost

Activities CY	13	14	15	16	17
Implement/Initiate RISCIS phase 2/3 clinical trial & NACTN PK study					
Enrollment into SCI registry					
Assessment of therapies for SCI					
Analysis of NACTN data for publication & presentation					
Estimated Budget ($K)		$.5M	$1.5M		

Updated: (May, 2015)

Goals/Milestones

CY13 Goals – Planning Phase 2/3 RISCIS/PK Clinical Study
☑ Publication of Riluzole Phase 1 clinical trial
☑ Protocol & infrastructure development of Phase 2/3 trial
☑ AOSNA/Reeve RISCIS Term Sheet signed
☑ Ongoing enrollment in SCI Registry
CY14 Goals – Implement Phase 2/3
☑ Collaboration/PK agreements signed
☑ Add PK protocol and DOD language to master protocol
☑ Submit FY 2014 JWMRP proposal to complete RISCIS/PK study
CY15 Goals – Enrollment in Phase 2/3
☑ Receive DOD Approval
☐ IRB regulatory approvals & site initiation meeting(s)
☐ Initiate patient enrollment; data entry; monitoring visits
☐ Follow-up visits, data entry
CY16 Goals - Continue Enrollment in Phase 2/3
☐ Follow-up visits, data entry
CY17 Goals – Complete Follow-up in Phase 2/3
☐ Analyze data; present data, publish manuscript
Comments – DOD approved master protocol, Sites receiving local IRB approvals
Budget Expenditure to date – Projected: $2,000,000 Actual : $740,888.00

9. Appendices

A. A Prospective, Multicenter, Phase I Matched-Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury Robert G. Grossman, Michael G. Fehlings, Ralph F. Frankowski, Keith D. Burau, Diana S.L. Chow, Charles Tator, Angela Teng, Elizabeth G. Toups, James S. Harrop, Bizhan Aarabi, Christopher I. Shaffrey, Michele M. Johnson, Susan J. Harkema, Maxwell Boakye, James D. Guest, and Jefferson R. Wilson, *Journal of Neurotrauma* 31:239-255 February 1, 2014

B. SCI Data Registry Summary, May 12, 2015

C. NACTN Data Dissemination Policy

D. Spine Injuries Sustained by US Military Personnel in Combat Are Different From Non-Combat Related Spine Injuries, Nicholas S. Szuflita, Chris J. Neal, Michael K. Rosner, MD, Ralph F. Frankowski, Robert G. Grossman, submission to *Military Medicine*

E. Rationale, design and critical endpoints for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): A randomized, double-blinded, placebo-controlled parallel multi-center trial, MG Fehlings, H Nakashima, N Nagosh, DSL Chow, RG Grossman, B Kopjar, *Spinal Cord* (2015), 1-8 1362-4393/15

F. ISCOS Abstract

G. Year 2 Quarter 4 Financial Report

APPENDIX A

JOURNAL OF NEUROTRAUMA 31:239–255 (February 1, 2014)

DOI: 10.1089/neu.2013.2969

A Prospective, Multicenter, Phase I Matched-Comparison Group Trial of Safety, Pharmacokinetics, and Preliminary Efficacy of Riluzole in Patients with Traumatic Spinal Cord Injury

Robert G. Grossman,[1,*] Michael G. Fehlings,[2,*] Ralph F. Frankowski,[3] Keith D. Burau,[3] Diana S.L. Chow,[4] Charles Tator,[2] Angela Teng,[4] Elizabeth G. Toups,[1] James S. Harrop,[5] Bizhan Aarabi,[6] Christopher I. Shaffrey,[7] Michele M. Johnson,[8] Susan J. Harkema,[9] Maxwell Boakye,[9] James D. Guest,[10] and Jefferson R. Wilson[2]

Abstract

A prospective, multicenter phase I trial was undertaken by the North American Clinical Trials Network (NACTN) to investigate the pharmacokinetics and safety of, as well as obtain pilot data on, the effects of riluzole on neurological outcome in acute spinal cord injury (SCI). Thirty-six patients, with ASIA impairment grades A–C (28 cervical and 8 thoracic) were enrolled at 6 NACTN sites between April 2010 and June 2011. Patients received 50 mg of riluzole PO/NG twice-daily, within 12 h of SCI, for 14 days. Peak and trough plasma concentrations were quantified on days 3 and 14. Peak plasma concentration (C_{max}) and systemic exposure to riluzole varied significantly between patients. On the same dose basis, C_{max} did not reach levels comparable to those in patients with amyotrophic lateral sclerosis. Riluzole plasma levels were significantly higher on day 3 than on day 14, resulting from a lower clearance and a smaller volume of distribution on day 3. Rates of medical complications, adverse events, and progression of neurological status were evaluated by comparison with matched patients in the NACTN SCI Registry. Medical complications in riluzole-treated patients occurred with incidences similar to those in patients in the comparison group. Mild-to-moderate increase in liver enzyme and bilirubin levels were found in 14–70% of patients for different enzymes. Three patients had borderline severe elevations of enzymes. No patient had elevated bilirubin on day 14 of administration of riluzole. There were no serious adverse events related to riluzole and no deaths. The mean motor score of 24 cervical injury riluzole-treated patients gained 31.2 points from admission to 90 days, compared to 15.7 points for 26 registry patients, a 15.5-point difference ($p = 0.021$). Patients with cervical injuries treated with riluzole had more-robust conversions of impairment grades to higher grades than the comparison group.

Key words: clinical trial; neuroprotection; riluzole; spinal cord injury

Introduction

There is currently no neuroprotective therapy that has emerged as a standard of care after traumatic spinal cord injury (SCI). After a traumatic injury, the spinal cord undergoes a prolonged series of biological processes of reaction and repair. Therapies have been directed toward limiting the damage to the spinal cord and enhancing repair at each stage of the process. The general categories of therapy have been neuroprotection to limit the secondary injury that occurs after acute trauma, modulating the inflammatory response to injury, modifying the glial and fibroblastic scar that blocks regrowth of axons, and stimulating regrowth

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[5]Department of Neurosurgery, Thomas Jefferson University, Philadelphia, Pennsylvania.
[6]Department of Neurosurgery, University of Maryland, Baltimore, Maryland.
[7]Department of Neurosurgery, University of Virginia, Charlottesville, Virginia.
[8]Department of Neurosurgery, University of Texas Health Science Center, Houston, Texas.
[9]Department of Neurosurgery, University of Louisville, Louisville, Kentucky.
[10]Department of Neurosurgery, University of Miami, Miami, Florida.
*Drs. Grossman and Fehlings share first author status.

and repair of damaged axons and providing substrates to guide axons and bridge gaps. Substantial repair of SCI will probably require the application of a series of therapies, each directed toward a particular phase of the reactive and reparative processes.

Early within the secondary injury cascade, the initial trauma force, in combination with subsequent ischemic changes, leads to neuronal membrane dysfunction, which includes the constitutive activation of voltage-gated sodium ion channels.[1–3] This pathologic continuous activation causes a marked increase in intracellular sodium levels and leads to an influx of calcium ions through the sodium-calcium exchange pump.[4,5] Rises in intracellular calcium concentration then lead to the extracellular release of toxic levels of the excitatory neurotransmitter glutamate.[6] The combination of these events leads to increased regional cellular death as a result of ionic imbalance, formation of reactive oxidative ions, intracellular energy failure, cytotoxic edema formation, and glutamatergic excitotoxicity.

Riluzole, a sodium-channel blocking medication, which is U.S. Food and Drug Administration (FDA) approved for the treatment of amyotrophic lateral sclerosis (ALS),[7] has been shown to improve the outcome of SCI in preclinical studies.[8,9] Twelve preclinical studies of riluzole efficacy in acute rodent models of SCI, published between 1996 and 2011, have recently been summarized in a review article on neuroprotective drug therapy and SCI.[10] In comparison to control animals, riluzole-treated animals exhibited reduced tissue cavitation and better preservation of white matter, motor neurons, mitochondrial function, somatosensory-evoked potentials, and locomotor scores in different studies.[10] Recent work evaluating the timing of riluzole administration in rats revealed that treatment initiated at both 1 and 3 h postinjury resulted in improved neurobehavioral outcomes as well as tissue-preserving effects.[11] The presence of a well-defined target mechanism and demonstration of beneficial effects in pre-clinical studies, combined with its tolerability in the ALS population, make riluzole an attractive candidate for evaluation to treat acute human SCI.[12] With this background, a phase I prospective, matched-comparison group trial of the pharmacokinetics (PK), safety, and preliminary efficacy of riluzole as a neuroprotective agent in acute traumatic SCI was carried out with the following goals to:

1. Test the feasibility of a trial of a therapy that must be administered within 12 h of acute traumatic SCI.
2. Study the PK and pharmacodynamics of riluzole in SCI.
3. Obtain data on the safety of riluzole in SCI using a matched cohort group for comparison.
4. Obtain exploratory pilot data on the effects of riluzole on measures of neurological outcome after SCI using a matched cohort group for comparison.
5. Relate the pharmacology of riluzole in SCI to safety and outcome measures.

Methods

Organization of the trial by the North American Clinical Trials Network

The trial was registered with ClinicalTrials.gov (identifier: NCT00876889). Planned enrollment of 36 patients was conducted between April 12, 2010 and June 20, 2011 at six clinical centers of the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury (Table 1). NACTN is a consortium of clinical centers composed of neurosurgery department faculty and staff caring for SCI patients at university-affiliated hospitals, a coordinating center, a data management center and a pharmacological center. Each NACTN clinical center has one or two principal investigators and a study coordinator who is a physician or a clinical research nurse. NACTN was established in 2005 with the support of the Christopher Reeve Foundation, which is its sponsoring organization.[13,14] The Telemedicine and Advanced Technology Research Center (TATRC), United States Army Medical Research and Materiel Command (USAMRMC), has supported NACTN since 2006. Partial grant support for this trial was also received from AOSpine, which helped to facilitate the trial design and initial logistics of trial implementation.

Table 1. Trial Sites

Trial sites	*Principal investigators*
Thomas Jefferson University, Philadelphia	James S. Harrop, MD
University of Maryland, Baltimore	Bizhan Aarabi, MD
University of Virginia, Charlottesville	Christopher I. Shaffrey, MD
University of Texas Health Science Center, Houston	Michele M. Johnson, MD
University of Louisville, Louisville	Susan J. Harkema, PhD Maxwell Boakye, MD
University of Toronto, Toronto	Michael G. Fehlings, MD, PhD Charles H. Tator, MD, PhD

Trial design: Riluzole treatment cohort and eligibility criteria

The trial was a multi-site, single-arm, open-label-treatment pilot study with an enrollment goal of 36 patients. Eligibility criteria are given in Table 2. A detailed description of the trial design has been

Table 2. Eligibility Criteria

Inclusion criteria
Age ≥ 18 and ≤ 70 years
Written informed consent by patient or legally authorized representative to participate in the study
No other life-threatening injury
Nonpenetrating spinal cord injury at neurologic level from C4 to T11
ASIA Impairment Scale grade A, B, or C
No cognitive impairment that would preclude an informed consent, including moderate or severe traumatic brain injury
Initial dose of riluzole within 12 h of injury
Exclusion criteria
Hypersensitivity to riluzole or any of its components
Unable to receive riluzole orally or by nasogastric tube
History of liver or kidney disease (e.g., hepatitis A, B, or C or cirrhosis)
A recent history of regular substance abuse (illicit drugs or alcohol)
Unconscious
Penetrating spinal cord injury
Pregnancy as established by urine pregnancy test
Currently involved in another spinal cord injury research study
Has a mental disorder or other illness, which, in the view of the site investigator, would preclude accurate medical and neurological evaluation
Unable to commit to the follow-up schedule
Is a prisoner
Unable to converse, read, and write in English at the elementary-school level

published previously.[15] The sample size of this safety study was established in advance and was based on complication rates observed in NACTN registry data[13] and discussed below. The incidence rates of complications were expected to range from 0.15 to 0.30 in patients not treated with riluzole. Using a one-sided exact binomial test with a type I error rate of 5%, a case series of 36 patients receiving riluzole was projected to have approximate power of 0.80–0.99 to detect doubling of the complication rate in the riluzole case series.

Comparison group: North American Clinical Trials Network Spinal Cord Injury Registry group

As a phase I trial, the study did not have a concurrent control group of patients who did not receive riluzole, but who otherwise received the same standard of care treatment as the riluzole cohort. In lieu of a concurrent control group with which to compare the safety and neurological outcome data for the riluzole cohort, a comparison group was formed of 36 SCI patients who had received standard-of-care treatment at the NACTN clinical centers, whose records were in the NACTN SCI Registry. The NACTN SCI Registry contains information about the clinical courses of 594 SCI patients admitted to the NACTN clinical centers from October 2005 through November 2012, who consented to having data on their injury recorded in an institutional review board (IRB)- and human research protection office (HRPO)-approved data registry. Information was collected prospectively under the following headings: demographic data; medical history; initial clinical status; Glasgow Coma Score (GCS); Abbreviated Injury Score; International Standards For Neurological Classification of Spinal Cord Injury (ISNCSCI) motor, sensory, and impairment scores; type of neurological injury; type of bony injury; imaging of cord and canal diameters on computed tomography, magnetic resonance imaging, or myelogram; traction-reduction; medical therapy; surgical therapy; complications, including cardiac, pulmonary, hematological, gastrointestinal (GI), genitourinary (GU); infectious; skin; and neuropsychiatric.[14]

Data from 36 registry patients meeting the eligibility criteria for the riluzole patients were matched with the 36 patients treated with riluzole. Criteria for registry cases included admission to a NACTN center within 12 h of injury, American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A, B, or C at admission, cervical or thoracic injury, nonpenetrating SCI at neurological level from C4 to C11, and GCS >13. Registry cervical and thoracic cases were then matched by AIS grade to the riluzole patients' neurological level of injury, gender, and age. This hierarchy of matching was the method adopted to select among multiple matches. All matching was blinded to outcome measures in the registry and riluzole groups. Thirty (83%) of the 36 registry patients were drawn from five of the six NACTN sites trialing riluzole in the present study.

Determination of riluzole dose and dosing schedule

Riluzole (50 mg; Rilutek®; Sanofi-Aventis, Bridgewater, NJ) was administered every 12 h orally or by nasogastric tube, starting within 12 h of injury for 28 doses.

The riluzole dose was determined by using human data and by scaling from animal data.[16] From the human data, the most conservative approach was used, based on the FDA-approved dose for ALS patients. In dose-ranging studies of riluzole in ALS that used doses of 50, 100, and 200 mg/day, a daily dose of 50 mg twice-daily (b.i.d.) of riluzole was confirmed to have the best benefit-to-risk ratio.[17]

From animal data, the human equivalent dose (HED) was allometrically scaled from the animal dose (6 mg/kg b.i.d.) in female Wistar rats (weight, 250–300 g) and was calculated with the equation from FDA Guidance for Industry (2005)[18]:

$$\begin{aligned}\text{HED} &= \text{Animal Dose (mg/kg)} \times (\text{animal wt/human wt in kg})^{0.33} \\ &= (6\ \text{mg/kg bid}) \times (0.25\ \text{kg}/70\text{kg})^{0.33} \\ &= 0.92\ \text{mg/kg bid} = 64.2\ \text{mg}/70\ \text{kg b.i.d.}\end{aligned}$$

The trial dose of 50 mg b.i.d. was set conservatively below the HED of 64.2 mg b.i.d., scaled from the effective, safe animal dose of 6 mg/kg b.i.d.[11] and in concordance with the dose of 50 mg b.i.d. that achieved the best safety and efficacy balance in ALS patients.[17]

The time window of 12 h after injury for administration of riluzole is in concordance with a study of delayed postinjury administration of riluzole in a preclinical model of moderate cervical SCI.[11] Riluzole treatment at 1 h and at 3 h postinjury both provided locomotor improvement. Differences in metabolic rate and time course of appearance of inflammatory biomarkers in rodents and humans suggest that pathological changes in SCI peak 4–6 times more rapidly in rat than in human SCI, making 12 h a reasonable exploratory time window for a phase I trial of riluzole.[11] The mean time and standard deviation (SD) of SCI patients receiving the first dose of riluzole in the present study was 8.7 ± 2.2 h.

Pharmacology of riluzole in spinal cord injury patients

The PK of riluzole in the 36 patients in the present study have been published in detail.[16] Plasma samples for PK study were collected 1–2 h predose and 2 h postdose for trough and peak concentrations, respectively, on days 3 and 14 after the initial dose. Findings that are pertinent to the phase I clinical trial are given below in the Results section of this report.

Patient care protocol

Patients received care for SCI as described in the *Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries*.[19] Treatment included rapid ventilatory, cardiovascular and nutritional support, reduction of vertebral subluxations, surgical decompression of the spinal cord and vertebral stabilization, and prophylactic measures to prevent deep vein thrombosis (DVT) using leg compression devices and/or anticoagulation with heparin or low molecular weight heparin. Administration of corticosteroids, generally methylprednisolone (MPSS), was in accord with the policies of the admitting center. Thirty–nine percent of the riluzole and 58% of the registry patients received MPSS.

Schedule of events and data collection

Table 3 shows the schedule of events for the study, the riluzole dosing schedule, and the clinical and laboratory data that were collected on admission to the study, during acute hospitalization, and at 42 ± 7, 90 ± 10, and 180 ± 14 days.

Screening and admission to the study

SCI patients examined in the emergency department (ED) within 12 h of injury were screened for eligibility and had the study explained to them and to legally authorized representatives, if present. Consenting individuals were then enrolled in the trial. Time of enrollment was taken as the time of admission to the study, and the measurements referred to in the tables as admission data were made at this time, before receiving riluzole. For the purpose of recording and tracking riluzole administration, the day on which the first dose of riluzole was given was designated as day 1 of the study.

Data collection

Data were collected prospectively, daily when required by the protocol, by NACTN clinical coordinators working together with the principal investigators of each clinical site. Data were recorded

TABLE 3. SCHEDULE OF EVENTS

	Screening (<12 hrs. from injury) Enrollment/ Admission	*Treatment Period*													*Post Treatment*	*Follow-up*			
		Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8*	*Day 9*	*Day 10*	*Day 11*	*Day 12*	*Day 13*	*Day 14*	*D/C Acute*	*Day 42*	*Day 90*	*Day 180*	*Unscheduled F/U*
Chart Review	X																			
Enrollment/Trial Admission	X																			
Informed Consent Form Signed	X																			
Identification Data	X																			
Medical History/SCI Data	X														X	X	X	X		X
ISNCSCI Examination	X			X																
Clinical Blood Draw/Liver Function Tests	X			X				X			X				X					
Pharmacology Blood Draw	X			Trough Peak											Trough Peak					
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Riluzole Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Adverse Events/ Complications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Discharge Data																X				
BPI Short Form																	X	X	X	X
SCIM version 1																	X	X	X	X

on 16 case-report forms, throughout the course of the acute care hospitalization of the patients and at the follow-up visits made in the rehabilitation hospital or at the clinical center. The following data were collected:

1. Prehospitalization demographic data, past medical history, preinjury medication use, circumstances and time of injury, and time of arrival to the ED of the admitting NACTN hospital.
2. Evaluation of the medical condition of the patient.
3. Measurement of neurological status with ISNCSCI motor and sensory and AIS examinations.[20] Evaluations were repeated on days 3 and 14 of acute hospitalization, before and after spinal surgery, and at the 42-, 90-, and 180-day examinations. The Spinal Cord Independence Measure (SCIM)[21] was performed at 90 and 180 days.
4. Details of the medical and surgical therapy received.
5. Hematology and blood chemistries, including liver function tests, were drawn on admission to the study and on days 3, 7, 10, and 14 and when medically indicated at 42, 90, and 180 days.
6. Medical complications and serious adverse events (SAEs) were assessed by NACTN principal investigators by observation of the patients with input of the clinical coordinators as well as medical and nursing staff. Categorization and severity level of complications were determined by the principal investigators using the criteria described in an analysis of the incidence and severity of acute complications after SCI, based on data from the NACTN SCI Registry.[22]

All data were submitted to the data management center and were subjected to multiple manual and electronic data quality-control procedures.

Compliance with regulatory requirements

1. Approval of the protocol by the HRPO of the Department of Defense (DoD).
2. Harmonization of the IRB requirements of each center with requirements of the HRPO; final approval of the harmonized protocol and the informed consent form by each IRB.
3. Appointment of a central trial medical monitor, a physiatrist at a university unaffiliated with any of the centers, who received reports of all SAEs.
4. Appointment of a local medical monitor at each clinical center who received reports of adverse events at that center.

Training of personnel and trial initiation meeting

Two training meetings were held at the Frazier Rehab Institute for the principal investigators and study coordinators, reviewing in detail the study protocol, the *Guidelines for the Management of Acute Cervical Spine and Spinal Cord Injuries*[19] and in performing ASIA examinations on individuals with SCI under the guidance of skilled instructors.

A trial initiation meeting of all investigators and coordinators was held at The Methodist Hospital Coordinating Center, including a 2-day review of the protocol, the schedule of events, the rules and procedures for reporting adverse events, and stopping rules.

Site monitoring

NACTN's study monitor conducted on-site visits to the clinical centers and reviewed case report forms, source documentation, and on-site regulatory binders to ensure regulatory and protocol compliance with Good Clinical Practices.

Statistical analysis

Admission characteristics of riluzole and registry patients were compared using two-sample independent *t*-tests and two-sample chi-square methods or Fisher's exact test, as appropriate, for categorical data. Chi-square methods were also used to compare the incidence of medical complications between the two groups. Total motor scores for riluzole and registry patients stratified by impairment grade at admission were analyzed using the permutation test for independent samples, with motor scores as the raw observations. The permutation test makes no assumptions about the shapes of the underlying distributions or dispersions of motor scores and is particularly effective for skewed data. Permutation tests were computed using StatXact 8 with Cytel Studio software (Cytel Inc., Cambridge, MA).

Box plots were used to compare distributions of 90- and 180-day gains in total motor score and pin-prick sensory scores for the riluzole and registry groups. Box plots show the middle 50% of the data by a box that extends from the 25th to the 75th percentile and tails (whiskers) that contain at least 99% of the data and markers that indicate any outlying data values. Sample medians are shown within each box. Box plots are labeled for ease in interpretation and comparison. All graphics and other statistical tests were computed using StatCorp (2009) Stata statistical software (Release 11; StataCorp LP, College Station, TX).

Results

The enrollment goal of the study was fulfilled. Thirty-six patients with acute traumatic injury to the spinal cord (ages, 18–69),

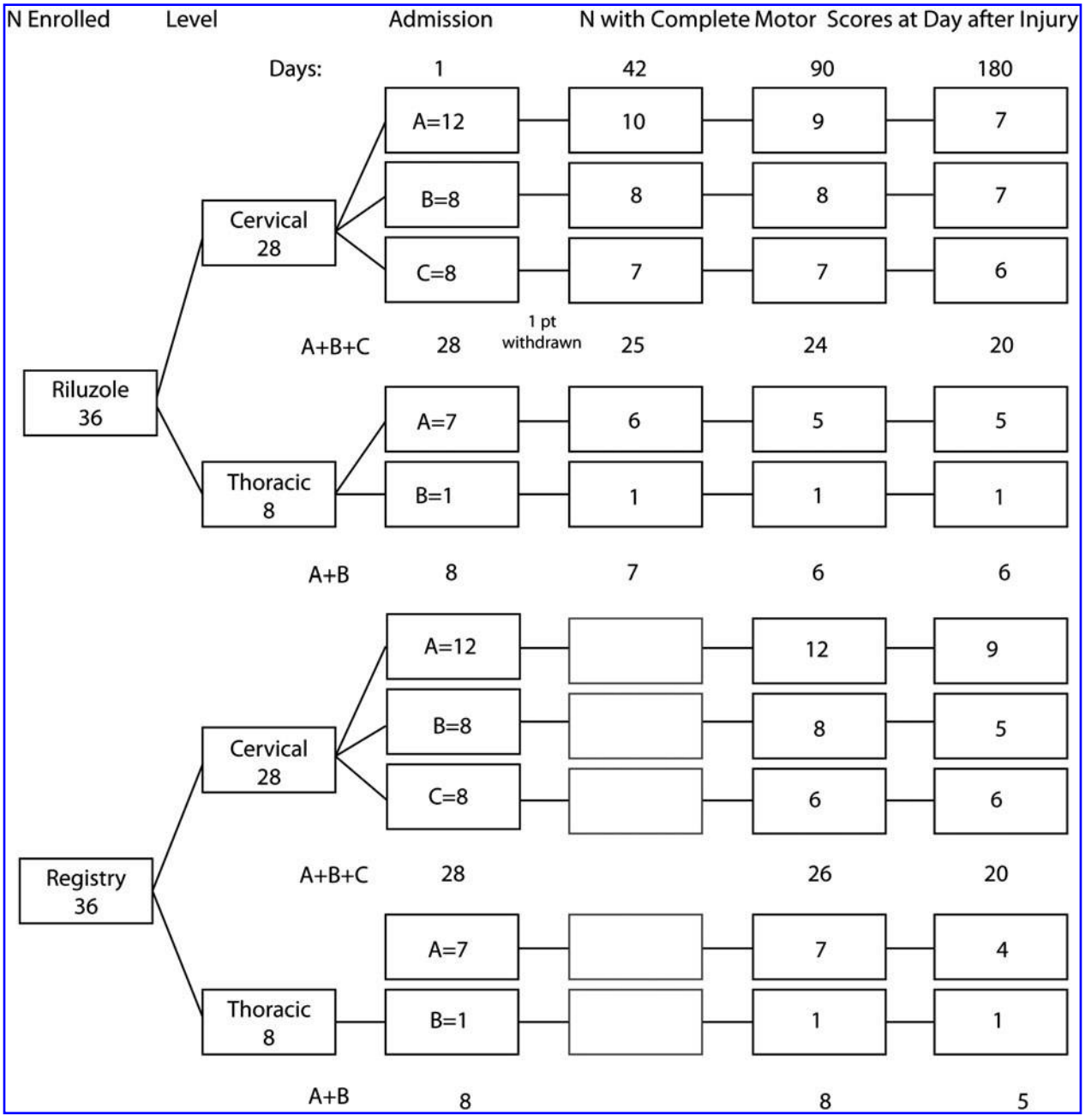

FIG. 1. Patient flow diagram of numbers of riluzole and registry patients available with complete motor scores on admission and at 42, 90, and 180 days.

impairment grades A–C, with levels of injury (lowest normal motor level) C4-T11, were enrolled at six NACTN clinical center hospitals between April 12, 2010 and June 20, 2011 and received riluzole enterally within 12 h of injury at a dose of 50 mg every 12 h for a total of 28 doses.

Cervical and thoracic injuries—riluzole and registry cohorts: Impairment grade on admission, demographics, cause of injury, hours to admission to emergency department and surgery, and corticosteroid administration

Figure 1 provides an overview of patient flow for safety and neurological outcome data, stratified by cervical and thoracic sites of injury and impairment grade. There were no statistically significant differences in demographics or clinical variables for the riluzole and registry patient groups (Table 4). Table 4 shows that 28 (78%) injuries in the riluzole cohort were cervical and 8 (22%) were thoracic.

Patients in the registry cohort were selected to match the numbers of cervical and thoracic injuries, neurological levels of injury, and impairment scale grades of the patients in the riluzole cohort. Distribution of impairment grades for both the riluzole and the registry cohorts was 19A, 9B, and 8C. Thirty (83%) patients were male and 6 (17%) were female in the riluzole cohort. The gender ratio was nearly identical in the registry cohort. The mean age was 41.3 years for patients with cervical injuries and 45.4 for patients with thoracic injuries, with a range of 18–69 in the riluzole cohort. The mean age for the cervical injuries in the registry cohort was 40.8 years. The causes of injury were predominantly motor vehicle accidents ($N=20$) and falls ($N=9$) in the riluzole cohort; the causes in the registry cohort were similar. Mean hours from injury to ED were 3.0 ± 1.8 for riluzole patients with cervical injuries and 2.5 ± 2.3 for registry patients.

Table 4. Cervical and Thoracic Injuries: Demographics and Clinical Variables on Admission To Study in Riluzole and Registry Patients

Variable	*Riluzole Cervical* N=*28*	*Registry Cervical* N=*28*	p *value*	*Riluzole Thoracic* N=*8*	*Registry Thoracic* N=*8*
AIS					
A	12	12		7	7
B	8	8		1	1
C	8	8		0	0
Total	28	28	Matched	8	8
Age in years	41.3 ± 17.4	40.8 ± 14.4	0.91	45.4 ± 16.4	30.4 ± 17.7
Gender					
Male	24	23		6	8
Female	4	5		2	0
Total	28	28	1.00	8	8
Cause					
Motor vehicle accident	13	8		7	6
Fall	8	11		1	2
Sports	5	8		0	0
Assault	2	1		0	0
Total	28	28	0.52	8	8
Hours to hospital ED	3.0 ± 1.8	2.4 ± 2.3	0.28	3.6 ± 1.7	2.7 ± 2.9
Surgery					
Yes	25	28		8	8
No	3	0		0	0
Total	28	28	0.24	8	8
Hours to surgery					
6–12	14	11		1	2
12–24	7	9		3	2
24–48	3	3		4	3
>48	1	5		0	1
Total	25	28	0.42	8	8
Body mass index	26.4 ± 4.1	27.0 ± 4.2	0.59	28.1 ± 4.3	26.1 ± 1.9
Surgical approach					
Anterior	4	7		0	1
Posterior	7	10		5	7
Both	14	11		3	0
Total	25	28	0.52	8	8
Corticosteroids					
Yes	10	17		4	4
No	18	11		4	4
Total	28	28	0.11	8	8

AIS, American Spinal Injury Association Impairment Scale; ED, emergency department.

Thirty-three (92%) of the riluzole patients underwent early surgery for spinal cord decompression and vertebral column stabilization, 42% within 6–12 h of injury, and another 28% in 12–24 h. Three of the cervical injuries did not undergo surgery. Median hours from injury to surgical decompression and stabilization were 11.3 h for cervical injuries and 23.6 for thoracic injuries for the riluzole cohort and were similar for the registry cohort. Surgical approaches were anterior (4; 12%), posterior (12; 36%), and both (17; 51%) for the riluzole cohort and were similar for the registry group.

Corticosteroids were administered at the time of admission to 39% of the riluzole cohort and 58% of the registry group.

The mean duration of initial hospitalization of the riluzole cohort was 17 days (range, 5–41). Thirty-five patients were discharged to a rehabilitation hospital and 1 to a nursing facility. The mean duration of hospitalization for the registry cohort was 23 days.

The leading pre-existing medical conditions in the riluzole cohort were hypertension (10 patients) and diabetes mellitus (5 patients) and were similar in the registry cohort.

Neurological levels of injury for cervical and thoracic patients receiving riluzole and for registry patients are shown in Table 5.

Table 5. Cervical and Thoracic Injuries: Riluzole and Registry Patients: Neurological Levels of Injury

Level of injury	N *(%)*	*% of cervical*
Riluzole cervical N = *28*		
C4	13 (36.1)	46.4
C5	7 (19.4)	25.0
C6	7 (19.4)	25.0
C8	1 (2.8)	3.6
Total cervical	28 (77.8)	(100)
Level of injury	N *(%)*	*% of thoracic*
Riluzole thoracic N = *8*		
T1	2 (5.6)	25.0
T2	2 (5.6)	25.0
T6	1 (2.8)	12.5
T9	1 (2.8)	12.5
T11	2 (5.5)	25.0
Total thoracic	8 (22.2)	(100)
Total cervical and thoracic	36 (100)	
Level of injury	N *(%)*	*% of cervical*
Registry cervical N = *28*		
C4	11 (30.6)	39.3
C5	10 (27.8)	35.7
C6	6 (16.7)	21.4
C8	1 (2.8)	3.6
Total cervical	28 (77.8)	(100)
Level of injury	N *(%)*	*% of thoracic*
Registry thoracic N = *8*		
T1	3 (8.3)	37.5
T6	2 (5.5)	25.0
T10	1 (2.8)	12.5
T11	1 (2.8)	12.5
T12	1 (5.5)	12.5
Total thoracic	8 (22.2)	(100)
Total cervical and thoracic	36 (100)	

For the patients with cervical injuries in the riluzole cohort, C4-level injuries predominated ($N = 13$; 46% of cervical injuries), followed by C5 and C6 ($N = 7$; 25% each) and C8 ($N = 1$; 4%). Among the thoracic injuries, 4 (50%) were high thoracic, at T1 and T2, respectively, 2 (25%) were mid-thoracic, at T6 and T9, and 2 were low thoracic, at T11. Seven of the eight thoracic injuries were impairment grade A on admission and one was B. Levels of injury were similar for riluzole and registry patients.

Distribution of impairment grades on admission for each level of injury for patients receiving riluzole is shown in Table 6. Distribution was similar for registry patients.

Time to riluzole administration and number of doses received

The mean time to the first dose of riluzole was 8.7 h for the riluzole cohort ($n = 36$) as a whole (Table 7). Thirty-five patients completed the study. The goal of administering 28 doses of riluzole was reached in 71% of these 35 patients; an additional 26% received 27 doses and 3% received 26 doses.

Patient withdrawal

One patient was withdrawn on the seventh day of receiving riluzole when his liver function tests showed a moderate elevation of gamma-glutamyl transpeptidase (GGT). This patient was a 69-year-old man with previous comorbidities of emphysema and hypertension. He had sustained a C4 injury in a fall (impairment grade C). He developed respiratory failure on day 2 and pneumonia on day 4. GGT was normal on admission and on day 4, but had risen to 4.6 × the upper limit of normal (ULN) on day 7. He was receiving medications that can impair liver function. Riluzole was stopped as a precautionary measure to prevent possible liver damage. GGT fell to a mildly elevated level on day 10. Impairment grade was C at 90 days postinjury and GGT was normal.

Pharmacokinetics of riluzole in spinal cord injury patients

A detailed report of the PK of riluzole in the patients in this study has been published.[16] The following will summarize the key data that are of pertinence to the current report. Riluzole PK were evaluated in 33 patients on day 3 and in 32 patients on day 14, as

Table 6. Cervical Injuries: Riluzole and Registry Patients: Neurological Level and Distribution of Impairment Grades on Admission

Level	*A*	*B*	*C*	*Total*
Riluzole: impairment grade				
C4	5	4	4	13
C5	2	3	2	7
C6	4	1	2	7
C8	1	0	0	1
Total	12	8	8	28
Registry: impairment grade				
C4	5	4	2	11
C5	2	3	5	10
C6	4	1	1	6
C8	1	0	0	1
Total	12	8	8	28

Table 7. Cervical and Thoracic Injuries: Time to Riluzole Administration

Time window	*Minimum (h)*	*25th percentile (h)*	*Median/mean (h) (SD)*	*75th percentile (h)*	*Maximum (h)*
Injury to admission $N=36$	0.7	1.5	2.3/3.0 (1.8)	4.2	7.0
Injury to riluzole $N=36$	3.7	6.9	8.5/8.7 (2.2)	10.6	12.1

SD, standard deviation.

both C_{peak} and C_{trough} samples of patients were collected and quantifiable. The plasma concentration and the systemic exposure to riluzole (area under the plasma-concentration curve; AUC_{0-12}) varied significantly among patients. Maximum concentration (C_{max}) ranged from 24 to 409 ng/mL (mean, 129 ± 14; standard error [SE]) on days 3 and 9 to 317 ng/mL (mean, 77 ± 14; SE) on day 14.

The PK of riluzole—C_{max}, C_{min}, AUC_{0-12}, clearance (CL), and volume of distribution (V)—changed during the acute and subacute phases of SCI during the 14 days of administration, a phenomenon consistently observed in all patients at all clinical sites. Mean C_{max}, C_{min}, and AUC_{0-12} (129 ng/mL, 46 ng/mL, and 982 ng*h/mL, respectively) were significantly higher on day 3 than on day 14 (77 ng/mL, 19 ng/mL, and 521 ng*h/mL, respectively), resulting from lower CL (50 vs. 106 L/h) and a smaller V (557 vs. 1298 L) on day 3.[16]

Safety: Medical complications and serious adverse events

SCI patients have a high incidence of physiological disturbances and medical complications occurring acutely after injury as documented in a recent publication of data from the NACTN SCI Registry.[22] Using the definitions of severe and moderate complications described in that article, the incidence of complications occurring within 30 days of injury was determined. Table 8 shows medical complications and SAEs tabulated both by frequency of occurrence of specific types of complications (e.g., infection and pulmonary) and by the number of individuals sustaining one or more complication. Complications reported as SAEs are marked with a superscript b.

Table 9 shows the number of patients in the riluzole and registry groups who sustained at least 1 complication involving one or more of the seven organs or systems by which complications were classified and the incidences of these complications. There was no significant difference between the two groups.

The frequency of specific types of severe and moderate complications, expressed as a percentage of the total number of complications, was also compared to that reported in 315 patients in the NACTN SCI Registry.[22] For riluzole versus registry, the comparisons were the following: infection, including pneumonia (26 vs. 22%); pulmonary, including pulmonary embolism, respiratory failure, lobar collapse, atelectasis, and pneumothorax (23 vs. 27%); hematological, including DVT, anemia, thrombocytopenia, and coagulopathy (12 vs. 15%); cardiac, including asystole, bradycardia, arrhythmia, and shock (7 vs. 13%); neurological/psychiatric, including neuropathic pain and depression and anxiety (15 vs. 7%); GI/GU, including bleeding and bowel obstruction (11 vs. 9%); and skin, including pressure sores (8 vs. 7%).

There were no SAEs attributable to riluzole. There were no deaths.

Table 8. Cervical and Thoracic Injuries: Riluzole Patients[a]

Complications	*No. of complications*
Infection: 19 complications (14 patients)	
Urinary tract infection	10
Pneumonia	5
Staphylococcal infection of skin	2
Sepsis[b]	1
Infectious diarrhea	1
Pulmonary: 17 complications (11 patients)	
Respiratory failure	7
Lobar collapse/atelectasis	3
Pneumothorax	2
Acute respiratory distress syndrome[b]	2
Pleural effusion	1
Bronchial obstruction mucus plug, syncope[b]	1
Pulmonary embolus[b]	1
Neurological/psychiatric: 11 complications (10 patients)	
Neuropathic pain	4
Depression	3
Anxiety	2
Agitation	1
Elevation of sensory level[b]	1
Hematological: 9 complications (7 patients)	
Deep venous thrombosis[b]	3
Thrombocytopenia	2
Neutropenia	1
Coagulopathy	1
Thrombophlebitis	1
Severe anemia	1
Gastrointestinal: 7 complications (5 patients)	
Prolonged nausea/vomiting	3
Rectal hemorrhage[b]	1
Dysphagia	1
Anal fistula	1
Bowel obstruction[b]	1
Skin: 6 complications (4 patients)	
Pressure-damaged skin areas other than sacral	3
Sacral decubiti	2
Rash: allergic reaction	1
Cardiovascular: 5 complications (5 patients)	
Prolonged arrhythmia	2
Asystolic episode[b]	1
Prolonged bradycardia (< 50 bpm)	1
Prolonged shock (BP < 80 mmHg)	1

[a]Seventy-four severe and moderate medical complications and 12 serious adverse events within 30 days of admission in 36 patients.
[b]Reported as a serious adverse event (total, $N=12$).
bpm, beats per minute; BP, blood pressure.

Table 9. Cervical and Thoracic Injuries: Riluzole and Registry Patients: Incidence of Medical Complications and *P* Values of Differences

	Riluzole N = *36*		*Registry* N = *36*		
System/category	*Patients*[a]	*Incidence*[b]	*Patients*[a]	*Incidence*[b]	p *value**
Infection	14	0.389	13	0.361	0.81
Pulmonary	11	0.306	16	0.444	0.22
Neuropsychiatric	10	0.278	8	0.222	0.59
Hematological	7	0.194	9	0.250	0.57
Cardiovascular	5	0.139	11	0.306	0.09
GI/GU	5	0.139	9	0.250	0.19
Skin	4	0.111	3	0.083	0.69

[a]Number of patients with at least one complication of the specified system.
[b]Incidence of complications within 30 days of injury.
*Pearson's chi-square test for comparing two proportions.
GI, gastrointestinal; GU, genitourinary.

Safety: Elevation of liver enzymes and bilirubin above the upper limit of normal

Liver enzymes and bilirubin were monitored on admission and during administration of riluzole. On admission, elevated levels of different liver enzymes and bilirubin were found in 9–37% of patients. Thirteen percent of patients had mild (>ULN to 2.5×ULN) or moderate (>2.5–5×ULN) elevations of alanine transferase (ALT), 37% had mild or moderate elevations of aspartate transaminase (AST), 11% had mild elevations of GGT, and 9% had mild elevations of bilirubin (Table 10; Fig. 2). Some patients had elevation of a single enzyme, whereas others had two or three enzymes elevated.

During administration of riluzole, liver enzymes and bilirubin were monitored on days 3, 7, 10, and 14. Incidence of elevation of enzyme levels increased during administration of riluzole, with increasing frequency in the second week of administration. Seventy percent of patients had mild or moderate elevations of ALT and 63% of AST on at least one of the days of testing. One patient had a borderline severe elevation of ALT (6×ULN; (severe defined as >5–20×ULN). Another patient had a borderline severe elevation of AST (5.5×ULN). These elevations returned to normal at 3 and 6 months. Fifty-three percent of patients had mild or moderate elevations of GGT, and 1 patient had a borderline severe elevation of GGT (7×ULN). Seventeen percent had mild or moderate elevations of alkaline phosphatase (ALP). Fourteen percent had mild or moderate elevation of bilirubin (Table 10; Fig. 2).

No patient had elevated bilirubin on day 14, the last day of administration of riluzole. The appearance of an increased level of a liver enzyme was not necessarily followed by a progressive increase in the level of that enzyme. In many cases, the elevated concentration had returned to a normal level at the next date of testing. The elevation of one enzyme was not necessarily linked to the elevation of another enzyme.

No relationship was found between the C_{max} of riluzole and liver enzyme levels.

Table 10. Cervical and Thoracic Injuries: Liver Enzyme and Bilirubin Elevations at Admission and during Riluzole Administration[a]

	ALT N *(%)*	*AST* N *(%)*	*ALP* N *(%)*	*GGT* N *(%)*	*Bilirubin* N *(%)*
Admission before riluzole					
Normal	27 (87)	20 (62)	32 (100)	25 (89)	29 (91)
Mild[b]	3 (10)	8 (25)	0 (0)	3 (11)	3 (9)
Moderate[c]	1 (3)	4 (12)	0 (0)	0 (0)	0 (0)
Severe[d]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	31 (100)	32 (100)	32 (100)	28 (100)	32 (100)
While receiving riluzole					
Normal	10 (28)	12 (33)	30 (83)	15 (44)	31 (86)
Mild[b]	15 (42)	16 (44)	5 (14)	13 (38)	4 (11)
Moderate[c]	10 (28)	7 (19)	1 (3)	5 (15)	1 (3)
Severe[d]	1 (3)	1 (3)	0 (0)	1 (3)	0 (0)
Total	36 (100)	36 (100)	36 (100)	34 (100)	36 (100)

[a]See Figure 2.
[b]Mild: >ULN to 2.5×ULN.
[c]Moderate: >2.5–5×ULN.
[d]Severe: >5–20×ULN.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; ULN, upper limit of normal.

Neurological outcome

Neurological outcome was assessed with ISNCSCI total motor score progression, sensory score progression, impairment grade conversion, and SCIM. Each measure was assessed separately for cervical and thoracic injury cohorts and stratified by impairment grades A, B, and C.

Cervical injuries: Progression of motor scores from admission to 42, 90, and 180 days

A flow diagram of the subgroups of the riluzole and registry cohorts, stratified as described above and the number of patients with complete ISNCSCI motor data available for comparison on the specified days after injury, is shown in Figure 1.

After withdrawal of 1 patient (C4 level of injury impairment grade C, see above, ''Patient withdrawal''), there were 27 with cervical injuries available for measurement of motor scores. The impairment grades and numbers of these patients were A-12, B-8, and C-7. Motor score outcomes in the riluzole-treated cohort were compared with those in a matched cohort of patients drawn from the NACTN SCI Registry (Table 4). The progression of the total motor scores from admission to 42 days for the riluzole cohort, and to 90 and 180 days for the riluzole and registry cohorts, is shown in Table 11 and illustrated graphically in Figure 3. Table 11 shows the

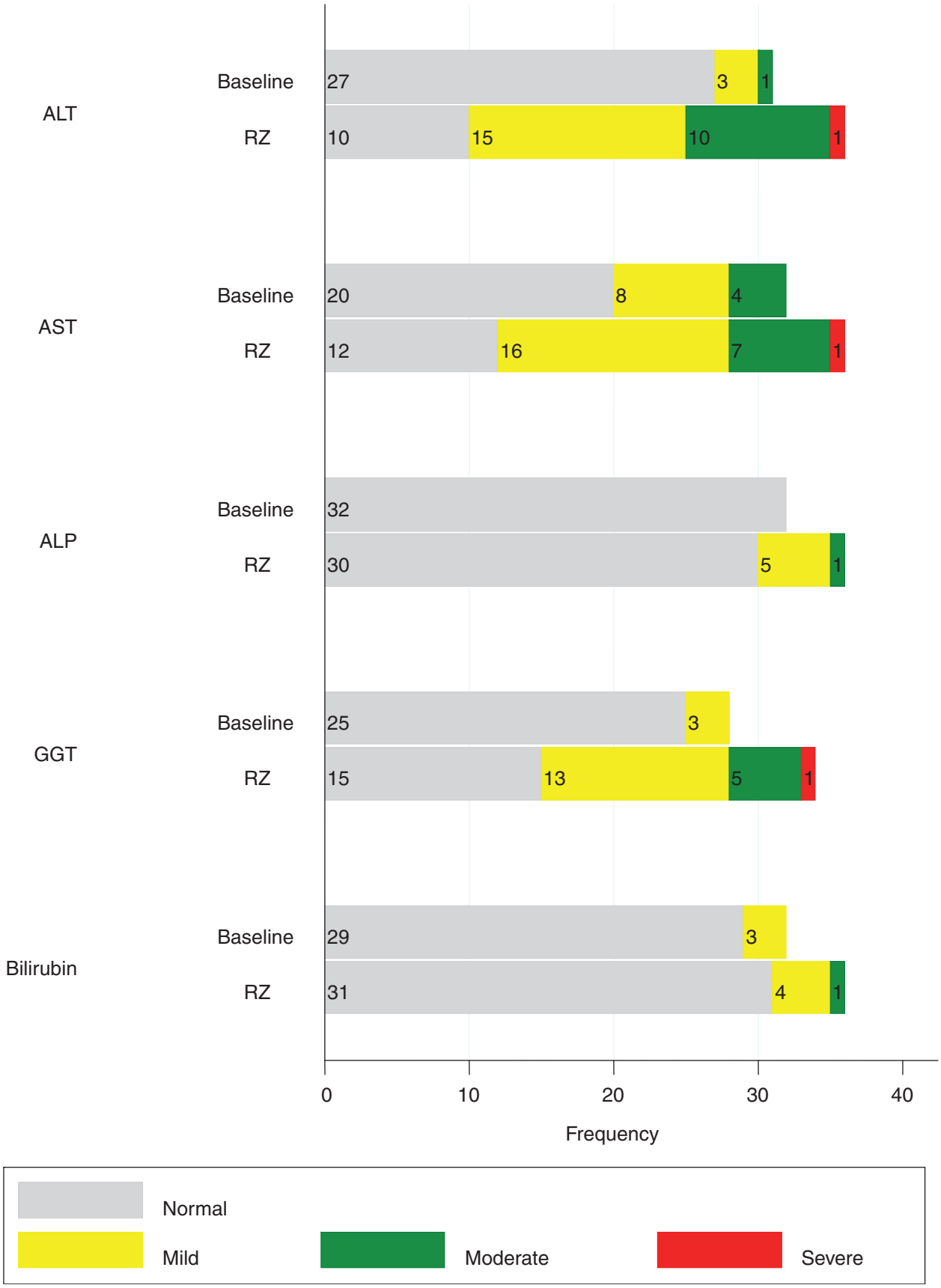

FIG. 2. Cervical and thoracic injuries: frequency of normal and elevated liver enzymes and bilirubin. See Table 10. ALT, alanine transferase; AST, aspartate transamine; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; RZ, riluzole.

Table 11. Cervical Injuries: Riluzole and Registry Patients

		Riluzole				
Admission	N	*Admission*[a] *mean (SD)*	*42-day mean (SD)*		*Registry*	
A	10	16.8 (15.9)	24.0 (16.1)			
B	8	16.4 (10.1)	44.5 (25.6)			
C	7	30.3 (23.0)	64.4 (28.1)			
All	25	20.4 (17.2)	41.9 (27.8)			
Admission to 90 days	N	*Admission*[b] *mean (SD)*	*90-day mean (SD)*	N	*Admission*[d] *mean (SD)*	*90-day mean (SD)*
A	9	14.6 (9.3)	27.3 (26.3)	12	21.6 (14.2)	31.9 (19.9)
B	8	16.4 (10.1)	55.4 (28.1)	8	19.9 (9.2)	31.0 (22.9)
C	7	30.3 (23.0)	76.1 (18.8)	6	36.7 (13.0)	68.8 (18.1)
All	24	19.7 (15.7)	50.9 (31.5)	26	24.5 (13.9)	40.2 (25.4)
Admission to 180 days	N	*Admission*[c] *mean (SD)*	*180-day mean (SD)*	N	*Admission*[e] *mean (SD)*	*180-day mean (SD)*
A	7	16.1 (8.7)	31.4 (29.6)	9	23.3 (13.8)	34.8 (20.8)
B	7	14.6 (9.4)	60.3 (24.6)	5	22.4 (11.1)	46.6 (32.5)
C	6	32.0 (24.5)	81.8 (23.9)	6	33.0 (13.9)	84.0 (12.3)
All	20	20.4 (16.6)	56.6 (32.5)	20	26.0 (13.4)	52.5 (30.3)

Sample size, mean, and standard deviation of motor scores at 42, 90, and 180 days are stratified by admission impairment grade (see Fig. 3). See consort diagram, Figure 1, and graph, Figure 3.

[a]Includes 25 riluzole patients with both an admission and 42-day motor score.
[b]Includes 24 riluzole patients with both an admission and 90-day motor score.
[c]Includes 20 riluzole patients with both an admission and 180-day motor score.
[d]Includes 26 registry patients with both an admission and 90-day motor score.
[e]Includes 20 registry patients with both an admission and 180-day motor score.
SD, standard deviation.

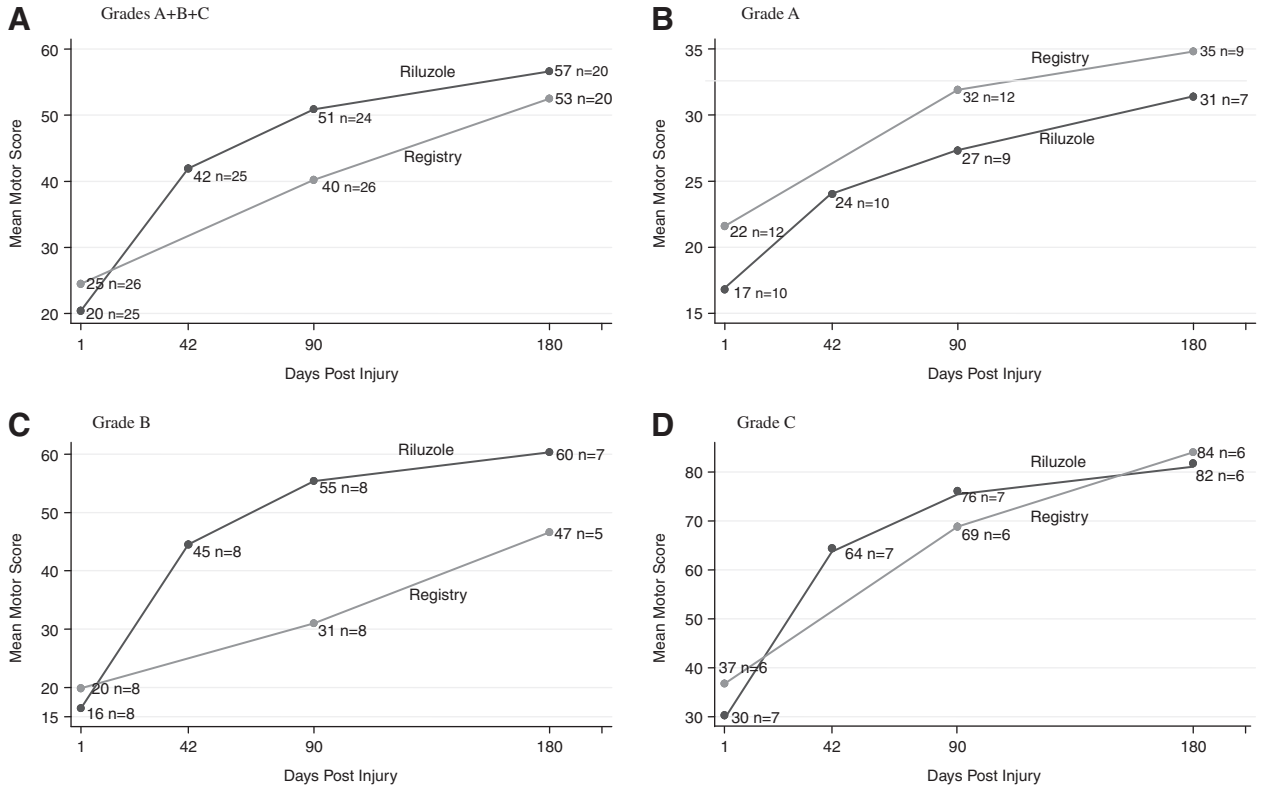

FIG. 3. Cervical injuries: riluzole and registry patients. Progression of mean total motor score (and *n* patients available) at admission and 42, 90, and 180 days, stratified by admission impairment grade. (**A**) All grades. (**B**) Grade A. (**C**) Grade B. (**D**) Grade C. See Table 11.

Table 12. Cervical Injuries: Riluzole and Registry Patients: Motor Score Mean Changes from Admission to 90 Days and from Admission to 180 Days

Admission AIS	N	*Riluzole 90-day change mean (SD)*	N	N	*Registry 90-day change mean (SD)*	*Riluzole: registry difference mean*	p *value**
A	9	12.7 (20.7)	12	12	10.3 (17.1)	2.4	0.787
B	8	39.0 (28.7)	8	8	11.1 (17.4)	27.9	0.037
C	7	45.8 (16.0)	7	6	32.1 (19.3)	13.7	0.194
All[a]	24	31.2 (26.2)	27	26	15.7 (19.3)	15.5	0.021
Admission AIS	N	*180-day change mean (SD)*	N	N	*180-day change mean (SD)*	*Riluzole: registry difference mean*	p *value**
A	7	15.3 (9.3)	7	9	11.4 (17.2)	3.9	0.715
B	7	45.7 (10.8)	5	5	24.2 (24.8)	21.5	0.208
C	6	49.8 (8.4)	5	6	51.0 (9.7)	–1.2	0.911
All[b]	20	36.3 (28.5)	18	20	26.5 (24.0)	9.8	0.248

[a]Includes all cases with both an admission and 90-day total motor score.
[b]Includes all cases with both an admission and 180-day total motor score.
*Exact *p* values based on the nonparametric permutation test for two independent samples.
AIS, American Spinal Injury Association (ASIA) Impairment Scale; SD, standard deviation.

absolute motor scores at admission and at 90 and 180 days, stratified by impairment grade on admission and for the cohort as a whole. Table 12 shows the *change* in scores from admission to 90 and to 180 days, stratified by impairment grade on admission and for the cohort as a whole.

Table 11 (upper panel) presents the progression of the mean total motor score for 25 riluzole patients with cervical injuries from admission to 42 days postinjury. The table includes only patients with admission and 42-day scores. Patients are stratified by impairment grades A, B, and C and by A + B + C, that is, the entire group taken as a whole (all).

Ten patients (admission impairment grade A) progressed from an admission mean motor score of 16.8 to 24.0 at 42 days, gaining 7.2 points and achieving 76% of the score of 31.4 reached at 180 days by 7 of these patients, as shown in the lowest panel of the table.

Eight patients (admission impairment grade B and motor score of 16.4) progressed to a score of 44.5 at 42 days, a gain of 28.1 points and achieved 74% of the score of 60.3 reached at 180 days by 7 of these patients.

Seven patients (admission impairment grade C and motor score of 30.3) progressed to a score of 64.4, a gain of 34.1 points, and achieved 79% of the score of 81.8 reached at 180 days by 6 of these patients.

For all grades, the group of 25 riluzole patients had a mean admission motor score of 20.4, progressed to a score of 41.9 at 42 days, a gain of 21.5 points, and achieved 74% of the score of 56.6 reached at 180 days by 20 of these patients, as shown in the lowest panel of the table.

The progression of motor scores to 90 and to 180 days for riluzole patients and registry patients, stratified by impairment grades, is shown in the middle and lowest panels, respectively, of Table 11 and is displayed graphically in Figure 3.

Table 11 (middle panel) compares the motor scores for 24 riluzole and 26 registry patients at 90 days postinjury, stratified by impairment grade. The table includes only patients with motor scores for those dates. Data for both the riluzole and registry groups, each taken as a whole (all), are shown in the lowest row of the panel and are displayed graphically in Figure 3A. For the 90-day comparison, the scores on admission were 19.7 for the riluzole cohort and 24.5 for the registry cohort. At 90 days, the riluzole cohort had progressed to a score of 50.9 and the registry cohort to a score of 40.2.

The lowest panel shows the scores at 180 days. At 180 days, the motor score for all patients was 56.6 for 20 riluzole patients and 52.5 for 20 registry patients.

The greatest gains in mean motor score occurred in grade B patients. The score of riluzole B patients went from 16.4 on admission to 55.4 at 90 days. At 180 days, the score of 7 riluzole B patients went from 14.6 to 60.3 (a 4.13-fold gain). The gain in bilateral lower extremity motor score (LEMS) exceeded that of the bilateral upper extremity motor score (UEMS). The gain in LEMS for 8 patients from admission to 90 days was 25.9 points and for UEMS, 13.1 points. The gain in LEMS for 7 patients from admission to 180 days was 29 points and for UEMS, 14.9 points.

The next-greatest gains were for C-grade patients, with a 2.45-fold gain at 90 days and 2.56-fold gain at 180 days. Grade A patients had the lowest gains (1.86-fold at 90 days and 1.95-fold at 180 days).

Table 12 presents the *change* of motor score and the riluzole cohort-registry cohort difference in the gain of scores and *p* values. The data are stratified by impairment grades and for the cohort as a whole for patients with admission and 90-day scores and patients with admission and 180-day scores.

For grade A patients, the riluzole-registry mean difference at 90 days was 2.4 points ($p = 0.787$); for grade B patients, 27.9 ($p = 0.037$); for grade C patients, 13.7 ($p = 0.194$). For the entire cohort, the difference was 15.5 (significant at $p = 0.021$). The score for the grade B patients contributed the largest effect toward the significance value for the entire group.

At 180 days, the riluzole-registry difference for grade B patients was 21.5 ($p = 0.208$) and for grade C patients, -1.2 ($p = 0.911$). For all patients, the difference was 9.8 ($p = 0.248$).

Figure 4 presents a box-plot comparison of the gains in motor scores from admission to 90 days for 24 riluzole patients and for 26 registry patients, as well as for 20 patients of each group at 180 days. Box plots show the median gain and the 75th and 25th percentiles and the maximum and minimum values for both groups. The median is used rather than the mean because the data are skewed toward higher motor score values, and thus a mean does not adequately locate the center of the data. This is particularly true for the 90-day gains. At 90 days, the median value was 23.5 for the

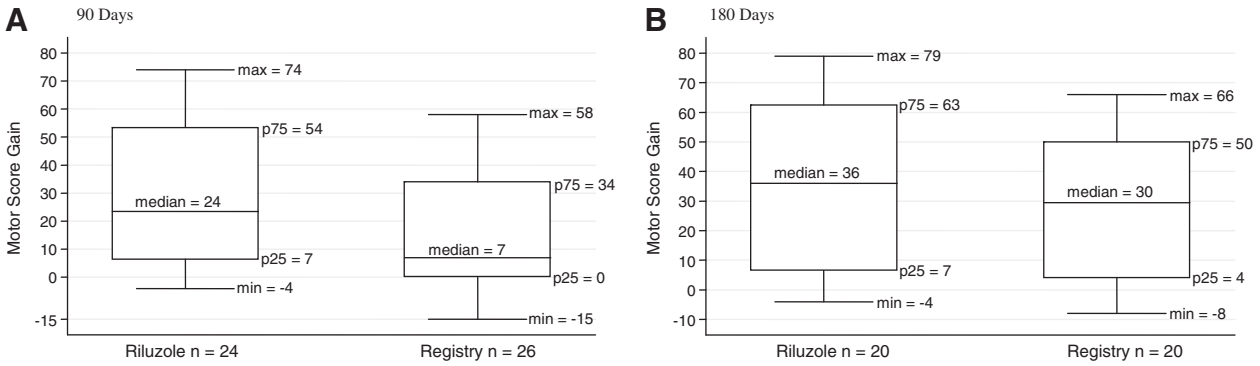

FIG. 4. Cervical injuries: riluzole and registry patients. Box plots of gains in total motor score. (**A**) 90 days. (**B**) 180 days. max, min, maximal and minimal scores encompassing at least 99% of the data; p25, p75, 25th and 75th percentiles.

riluzole group and 7 for the registry group. At 180 days, the median value was 36 for the riluzole patients and 29.5 for the registry patients. The distribution of the data indicates more robust motor outcome in the riluzole patients.

No relationship was found between gain in motor score and time from injury to administration of riluzole.

No differences were found in outcome motor scores between the 14 patients (cervical and thoracic) who received both MPSS and riluzole and patients who received only riluzole.

Cervical injuries: Progression of sensory scores

Pin-prick scores were available at 90 days for 24 riluzole patients and for 23 registry patients, as well as at 180 days for 20 riluzole and 15 registry patients. Box plots of gain in pin-prick scores for riluzole and for registry patients at 90 and 180 days are shown in Figure 5 as an example of the changes that were observed for both light touch and for pin-prick sensation. Pin-prick scores were 10 points higher for the riluzole patients than for the registry patients at 90 days and 9 points higher at 180 days for the riluzole patients than for the registry patients, but the differences in gains were not significant. The results for light touch were similar.

Cervical injuries: conversion of impairment grades at 90 days and at 180 days

Table 13 shows the change in impairment grades from admission to 90 days for 27 patients with cervical injuries and 26 matched registry patients. Of 12 grade A riluzole patients, 6 (50%) remained at A, 3 (25%) converted to B, 2 (17%) went to C, and 1 (8%) to D. In contrast, of 12 grade A registry patients, 9 (75%) remained at A and 1 (8%) each converted to B, C, and D.

Of 8 grade B riluzole patients, 1 remained at B, 3 converted to C, and 4 converted to D. In contrast, of 8 grade B registry patients, 4 (50%) remained at B, 3 (38%) converted to C, and 1 (12%) converted to D.

Of 7 grade C riluzole patients, 1 remained at C (14%), 5 (72%) converted to D, and 1 (14%) converted to E. In contrast, of 5 registry patients, 3 (60%) remained at C and 2 (40%) converted to D.

Table 14 shows conversions at180 days for 20 patients in the riluzole cohort and 20 in the registry cohort with impairment data. The percentage of patients that converted to a more functional grade continued to be higher in the riluzole than in the registry cohort. The greatest positive effect was in grade B patients.

Cervical injuries: Spinal Cord Independence Measure

SCIM scores were available at 180 days for 20 riluzole patients and for 14 registry patients. There was no significant difference in the total score for the entire riluzole cohort, in comparison to the registry cohort. Seven B grade patients, however, had a 17.8-point mean advantage over 5 grade B registry patients.

Thoracic injuries

There were 8 thoracic injuries: 7 grade A and 1 grade B. At 180 days, the group exhibited a mean gain of 3 points in total motor

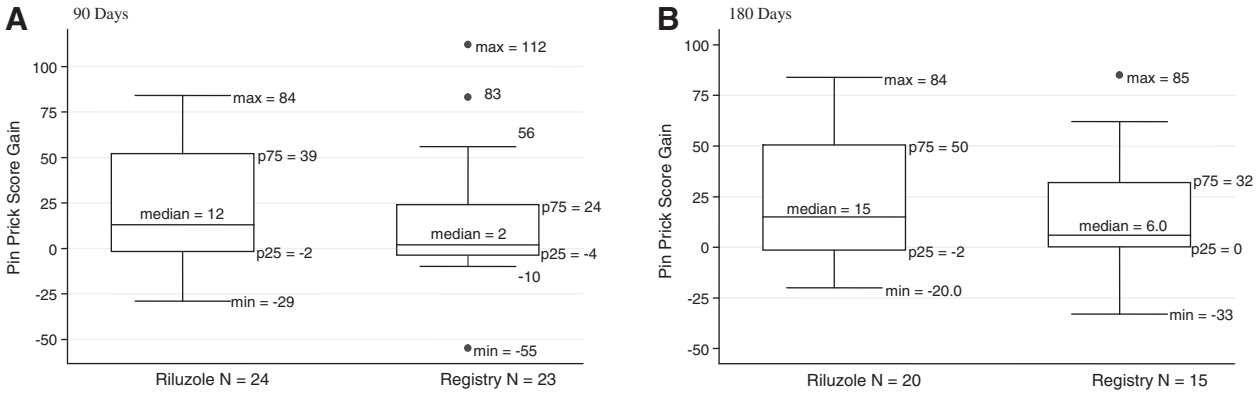

FIG. 5. Cervical injuries: riluzole and registry patients. Box plots of gains in pin-prick scores, all grades. (**A**) 90 days. (**B**) 180 days. max, min, maximal and minimal scores encompassing at least 99% of the data; ˙max, ˙min, outlying values; p25, p75, 25th and 75th percentiles.

Table 13. Cervical Injuries: Riluzole and Registry Patients

Riluzole

Admission		90 days				
		A	*B*	*C*	*D*	*E*
Grade	N = *27*	N *(%)*	N *(%)*	N *(%)*	N *(%)*	N *(%)*
A	12	6 (50)	3 (25)	2 (17)	1 (8)	
B	8		1 (13)	3 (37)	4 (50)	
C	7			1 (14)	5 (72)	1 (14)

Registry

Admission		90 days				
		A	*B*	*C*	*D*	*E*
Grade	N = *26*	N *(%)*	N *(%)*	N *(%)*	N *(%)*	N *(%)*
A	12	9 (75)	1 (8)	1 (8)	1 (8)	
B	8		4 (50)	3 (38)	1 (12)	
C	6			3 (50)	3 (50)	

Conversions of impairment grades at 90 days.

score and a 5.2-point gain in pin-prick score. Three of the 7 grade A patients converted to a more functional grade; 2 of the 7 matched registry grade A patients converted to a more functional grade.

Discussion

Feasibility of riluzole as an acutely administered therapy for spinal cord injury

The study demonstrates that it is feasible to screen, consent, and enroll SCI patients in a clinical trial of drug therapy, obtain laboratory and radiological data, and start pharmacological therapy within 12 h of injury. This finding should provide encouragement for further trials of therapies that must be applied very rapidly after SCI.

Table 14. Cervical Injuries: Riluzole and Registry Patients

Riluzole

Admission		180 days				
		A	*B*	*C*	*D*	*E*
Grades	N = *20*	N *(%)*	N *(%)*	N *(%)*	N *(%)*	N *(%)*
A	7	5 (71)	1 (14)	0 (0)	1 (14)	0 (0)
B	7			2 (29)	5 (71)	0 (0)
C	6			1 (17)	4 (64)	1 (17)

Registry

Admission		180 days				
		A	*B*	*C*	*D*	*E*
Grades	N = *20*	N *(%)*	N *(%)*	N *(%)*	N *(%)*	N *(%)*
A	9	7 (78)	1 (11)	0 (0)	1 (11)	0 (0)
B	5		2 (40)	1 (20)	2 (40)	0 (0)
C	6			0 (0)	6 (100)	0 (0)

Conversions of impairment grades at 180 days.

Demographic and neurological characteristics of the riluzole cohort

The patients enrolled in the present trial were representative of the population of SCI admitted to NACTN center hospitals in the distribution of injuries between cervical and thoracic locations and in the distribution of their impairment grades. Cervical injuries comprised 78% of the patients in the present study (Table 5), and the ratio of cervical to thoracic injuries and their impairment grades were similar in the NACTN SCI Registry. Therefore, there does not appear to be selection bias of patients for the present trial.

Pharmacology of riluzole in spinal cord injury

It would be expected that for riluzole to have a therapeutic effect, a threshold level of blood-plasma concentration must be reached and that there is a therapeutic range of concentrations.

An aim of the present study was to determine whether an association could be observed between blood-plasma levels of riluzole and motor outcome scores, with the object of determining a therapeutic blood-plasma level of riluzole. The previously published report of the pharmacology of riluzole in the patients in this phase I trial indicated that on day 3 of administration, there was a 17-fold difference in maximal concentration of riluzole between the lowest and highest values (24–409 ng/mL) in different patients. The cause of the variability in blood levels is likely to be, in part, the result of differences in absorption of riluzole from the gut[16] and, in part, from variability in individual body mass index (Table 4). An attempt was made to correlate C_{max} and gain in motor and sensory scores for all cervical injury patients as a group and for A, B, and C subgroups. No significant correlation was found. However, there was a positive correlation for grade B patients when extreme, outlying motor score and C_{max} values were censored. It is possible that the low levels of plasma concentration of riluzole, in some patients, did not reach a threshold for efficacy. Considering the multiple factors that determine neurological outcome, it may be difficult to achieve a correlation. Further analysis will be undertaken in a phase II study with a larger number of patients in an attempt to validate a therapeutic effect and determine a therapeutic range of plasma concentration. If a therapeutic effect and range can be established, monitoring of plasma levels and adjustment of the enteral dose would be a rational approach to therapy.

The previous publication of the pharmacology of riluzole in SCI reported on the finding of an increase in the clearance and distribution of riluzole between the 3rd and 14th days of administration that resulted in a lower plasma concentration on day 14. This finding indicates that the changing physiology of the SCI patient can affect the metabolism of drugs and emphasizes the importance of monitoring changes in drug metabolism in SCI clinical trials for evaluating safety and efficacy data. It is also another factor that suggests the possible utility of monitoring blood levels of riluzole to adjust dosage.

Safety of riluzole in spinal cord injury: Medical complications and serious adverse events

The primary aim of the phase I trial was to determine the incidence of medical complications and SAEs in SCI patients receiving riluzole. The incidence and types of complications were similar in the riluzole patients and in the comparison registry group and in the larger NACTN SCI Registry.[22] There were no SAEs attributable to riluzole and no deaths. In the NACTN SCI Registry, mortality in 126 patients with impairment grade A was 8.7% (11 patients). The

leading causes of death were cardiac ($n=4$), pulmonary ($n=4$), and multi-organ failure ($n=2$). If the same mortality rate occurred among the 19 grade A patients in the present trial, an average mortality of 1.65 patients would be expected.

Safety: Effects on liver enzymes

Elevations of ALT and of AST are considered to be indicators of drug-induced damage to liver cells. Elevation of GGT is a less-specific indictor of drug-induced damage to the liver. Elevation of ALP is considered to be primarily an indicator of obstruction of the bile duct. Elevation of liver enzymes has been reported in patients with ALS undergoing treatment with riluzole.[17] Elevation of liver enzymes has been reported to occur acutely in patients with SCI[23] and in animal models of SCI, possibly resulting from impairment of blood flow to the liver.[24,25] In the present study, riluzole administration in SCI patients was associated with a mild to moderate elevation of blood levels of ALT, AST, GGT, ALP, and bilirubin, to a varying degree for each of these markers of liver function. Elevations of ALT, AST, and GGT that reached the lower levels of a severe elevation (>5–$20\times$ULN) occurred on one occasion in each of 1 patient for each of these enzymes. Enzyme elevations were transient and bilirubin levels were normal on the last day of riluzole administration. Mild and moderate elevation of ALT and AST in SCI patients, as reported by Shepard and Bracken,[23] was confirmed to occur within the first day of injury before administration of riluzole.

Neurological outcomes: Cervical injuries, motor scores

As a phase I trial whose primary aims were determining the PK and safety of riluzole, and without a concomitant control group, the trial was not designed or powered to detect significant changes in neurological outcome. Nevertheless, a trend was observed of a more robust outcome in riluzole-treated patients.

Comparison can be made with the results of the recently published phase II placebo-controlled, randomized trial of minocycline in acute SCI.[26] Minocycline administration was associated with a 14-point gain in motor score over placebo, and motor score recovery substantially reached a plateau after 3 months. In the present phase I trial, a gain of 15.5 points was found for the riluzole group of 24 patients over the comparison registry group of 26 patients. It is difficult to precisely determine the comparability of the minocycline and the riluzole treatment groups and of the registry comparison and the placebo control group with respect to the anatomical levels of injury, distribution of impairment scores, and numbers of patients. Putting the question of comparability aside, Figure 3 of the minocycline article, showing graphs of motor gains of minocycline and placebo patients, shows, for minocycline patients, a gain from admission to 190 days of approximately 28 points, and for placebo, a gain of approximately 14 points. This gain is comparable to the gain at 180 days in the present phase I riluzole trial of 31.2 points for 24 riluzole patients and of 15.7 points for 26 registry patients.

In the minocycline trial in patients with cervical injuries, LEMS had greater gains than UEMS. In the present study, the same observation was made for grade B patients with cervical injuries who received riluzole.

Comparison of gains in UEMS can also be made with a recent report of the extent of spontaneous motor recovery after traumatic cervical sensorimotor complete SCI.[27] Analysis of the Sygen trial and the European Multi-Center Study about SCI (EM-SCI) databases found a 10–11-point gain in UEMS at 1 year. The riluzole grade B patients, not as severely impaired as grade A patients, achieved a UEMS gain of 14.9 points at 180 days and a LEMS gain of 29 points.

Cervical injuries: Progression of sensory scores

In the minocycline trial, cervical motor-incomplete patients had pin-prick scores that were 14 points greater than placebo patients.[26] In the riluzole patients, complete and incomplete injuries in the present study had, at 180 days, a gain of 9 points over the registry patients.

Cervical injuries: conversion of impairment grades

The most robust conversions were exhibited by grade B patients. At 90 days, 87% of 8 grade B riluzole patients converted to a more functional grade, compared to 50% of 8 grade B registry patients. At 180 days, all 7 (100%) of grade B riluzole patients had progressed to a more functional grade, compared to 3 (60%) of 5 registry patients.

These findings can be compared to data in the recent publication of motor recovery of cervical SCI from the National Spinal Cord Injury Statistical Center (NSCISC) database. For grade B patients, from a baseline of 7 days or less, to 1 year, 34% remained at grade B and 67% converted to C (30%) and D (37%).[28]

Conversions of grade A patients were not as robust, and rates for riluzole and registry patients were comparable to those reported in the EM-SCI database: For grade A patients assessed within 2 weeks of injury with a final assessment at 1 year, 32% converted to a more functional grade.[29] These figures are in agreement with the NSCISC database figure of 30% conversion at 1 year[28] and correspond in the present phase I study to the conversion rate for 7 grade A riluzole patients of 29% at 180 days.

It should be noted, in making comparisons with these two studies,[28,29] that their baseline measurements were made within 1 week of injury in one study and within 2 weeks in the other. In the present study, baseline assessment of impairment grade was made within 12 h of injury. It is well recognized that within such a group of patients, spontaneous improvement may occur rapidly, which would result in a different classification of some of the patients in the group if the assessment had been made at 72 h. However, the registry group was also assessed within 12 h and should be an appropriate comparison group.

Cervical injuries: The Spinal Cord Independence Measure

At 180 days, there was no significant difference between the SCIM scores of the riluzole and registry groups, although there was a trend for better scores for grade B patients.

Improvement in functional outcome is, of course, the desired goal of therapy. Further detailed study of SCIM and other functional outcome measures in a phase II trial is warranted.

Thoracic injuries

The 8 thoracic injuries in the present study were all motor complete. On admission, 1 patient had sacral sensation. There was minimal improvement of motor and sensory score in this group of patients. A recent report of the neurological outcomes of 399 thoracic complete patients in the EM-SCI database found minimal motor and sensory improvement in this group of severely injured patients.[30] Motor improvement occurred predominantly in patients with low thoracic injury. There were only two such individuals in

the present riluzole study. Therefore, a therapeutic effect of riluzole might be detected in a larger number of low thoracic injuries and in patients who are grade B or C.

Limitations of the study

The trial was open label and the patients and examiners were aware of the treatment, factors that might result in a positive bias for riluzole treatment.

The outcomes of the patients receiving riluzole were compared with a recent historical group of patients in the NACTN SCI registry and not with a contemporaneous control group, as would occur in a phase II trial. However, the comparison registry group used to evaluate outcomes was treated at NACTN hospitals operating under the same standard-of-care protocol, and many riluzole and registry patients were evaluated by the same clinical teams, which may have reduced the variability of scoring of outcome measures.

Factors other than treatment with riluzole may have influenced neurological outcome. The very short time from injury to ED admission and supportive medical care and from injury to surgical decompression and stabilization for both the riluzole and registry patients may have had a therapeutic effect, when compared to historical studies performed at earlier times, when the incidence of decompression or stabilization surgery was not as great or carried out as urgently.

The number of patients was small, particularly when stratified by impairment scores. As commonly observed in longitudinal studies of acute SCI, the number of patients available for examination decreased as patients completed inpatient rehabilitation and returned to their homes or to a care facility far from a NACTN center: Despite strenuous efforts to obtain data from all patients unable to return to a center for examination, 3 of the 27 cervical injury patients who completed the 14-day course of riluzole treatment were unavailable for examination at 90 days, and an additional 4 were unavailable at 180 days, leaving 24 riluzole patients for analysis at 90 days and 20 at 180 days. The variability of neurological outcomes of SCI patients is great, particularly of grade C patients, and in a small sample, even 1 or 2 patients with extreme scores can bias the results.

Conclusion

Riluzole administered enterally within 12 h of SCI was well tolerated. There were no SAEs attributable to riluzole. Bearing in mind the limitations of the study, the exploratory pilot data suggest that riluzole may have a beneficial effect on motor outcome in cervical SCI that was manifest at 90 days postinjury. Improvement in lower extremity motor score appeared to be the primary effect. Further study of the PK, safety, and effects of riluzole on neurological outcome in acute traumatic SCI will be carried out in a phase II trial.

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Author Disclosure Statement

No competing financial interests exist.

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APPENDIX B

REEVE FOUNDATION
NORTH AMERICAN CLINICAL TRIALS NETWORK®

Attachment B
North American Clinical Trials Network

SCI Data Registry Summary
05/12/2015

Table 1. Registry Screening and Enrollment

Status	Number	Percent Total
Screened	1387	
Enrolled	762	55%
In Database	698	92%
Pending	64	8%

Table 2. Patient Demographics

Characteristic	Number (n=687)	Percent
Gender		
Male	547	79.6
Female	133	19.4
Age (yrs)		
< 20	33	4.8
20-65	534	77.7
>65	120	17.5
Race		
White	476	69.3
Nonwhite	211	30.7

Table 3. Circumstances of Injury

Circumstance	Number (n=670)	Percent
Fall	247	35.9
MVA	211	30.7
Recreation	67	9.8
Motorcycle/ATV	58	8.4
Assault	44	6.4
Other/Unk	27	3.9
Military	16	2.3

[1-] See text for circumstance details

Table 4. Severity of Neurological Deficit
Initial AIS Grade Within 7 days of injury

AIS Grade	Number	Percent
A	214	33.1
B	63	9.7
C	81	12.5
D	153	23.6
E	40	6.2
not available	96	14.8
TOTAL	647	

Table 5. Incidence of Complications

Complications	SCI Cases (n=687)	Percent
None	246	35.8
1	167	24.3
2	56	8.2
3	46	6.7
4+	172	25.0

Table 6. Acute Care Complications
Type, Frequency, and Incidence

Complication	Frequency n= 1774 (%)	Number of patients	Incidence Rate (n= 687 cases)
Pulmonary	410 (23.1)	210	30.6
Infection	367 (20.7)	208	30.3
Cardiac	305 (17.2)	238	34.6
Hematology	254 (14.3)	158	23.0
GI_GU	151 (8.5)	108	15.7
Skin	151 (8.5)	106	15.4
Neuropsychiatric	129 (7.3)	111	16.2
Failure Of Stabilization	7 (0.4)	7	1.1

Incidence rates = (# of patients with the complication type)/687

Table 7. Injury Type and SCI Region

Characteristic	Number (n=670)	Percent
Injury Type		
Blunt	538	80.3
Crush	84	12.5
Penetrating	36	5.4
Other	12	1.8
Injury Region[1]		
Cervical	504	73.3
Thoracic	137	19.9
Lumbar/Sacral	42	6.1
SCIWORA	3	0.4

[1]Highest level report when injury involved multiple levels

Table 8. Surgical by AIS Grade

Number of Patients (n=647)						
AIS[1] Severity	Posterior (%)	Anterior (%)	Both (%)	None (%)	Unk (%)	**Total**
A	114 (53.3)	50 (23.4)	31 (14.5)	15 (7)	4 (1.9)	214
B	29 (46.0)	20 (31.7)	9 (14.3)	4 (6.3)	1 (1.6)	63
C	46 (56.8)	23 (28.4)	6 (7.4)	4 (4.9)	2 (2.5)	81
D	56 (36.6)	61 (39.9)	17 (11.1)	16 (10.5)	3 (2.0)	153
E	16 (40.0)	4 (10.0)	1 (2.5)	18 (45.0)	3 (7.5)	40
Unknown	46 (47.9)	27 (28.1)	9 (9.4)	14 (14.6)	1 (2.5)	96
Total	307	185	73	71	11	647

[1] First AIS obtained within 7 days of injury.

Table 9. Steroid Use by Severity of Neurological Deficit Initial AIS Grade Within 7 days of Injury

Steroids (n=647)				
AIS Grade	**Yes (%)**	**No (%)**	**Unknown (%)**	**n**
A	100 (46.7)	113 (52.8)	1 (0.5)	214
B	34 (54.0)	27 (42.9)	2 (3.2)	63
C	38 (46.9)	42 (51.9)	1 (1.2)	81
D	66 (43.1)	86 (56.2)	1 (0.7)	153
E	4 (10.0)	36 (90.0)	0	40
Unknown	26 (27.1)	68 (70.8)	2 (2.1)	96

Table 10. Hospital Stay and Acute Care Discharge

Hospital Length of Stay	Number (n=687)	Percent
<8 days	157	22.9
8-14	205	29.9
15-21	106	15.4
>21	219	31.9

Discharge Status	Number (n=655)	Percent
Rehabilitation Hospital	480	73.3
Home	109	16.6
Nursing home	20	3.1
In Hospital Death	18	2.7
Long term acute care facility	16	2.4
Other	12	1.8

Table 11. AIS Severity Conversion Admission versus Acute Care Discharge

	AIS[2] Discharge					
AIS[1] Admit	A	**B**	**C**	**D**	**E**	**Patients**
A	87.9%	7.4%	4.2%	0.5%	0.0%	190
B	11.7%	58.3%	25.0%	5.0%	0.0%	60
C	1.3%	4.0%	61.3%	32.0%	1.3%	75
D	0.7%	0.0%	2.0%	90.6%	6.7%	149
E	0.0%	0.0%	0.0%	8.1%	91.9%	37
Patients	176	52	72	166	45	511

[1]First AIS obtained within 7 days of injury: excludes cases with AIS unknown within 7 days of Injury

[2]AIS within 14 days of discharge from acute care: excludes cases with AIS unknown at discharge

Table 12. AIS Severity Conversion Admission versus Six-Month Follow-up

	Six Month AIS[2]					
AIS[1] Admit	**A**	**B**	**C**	**D**	**E**	**Patients**
A	70.9%	16.4%	7.3%	5.5%	0%	110
B	12.5%	25.0%	28.1%	28.1%	6.3%	32
C	5.0%	5.0%	12.5%	60.0%	17.5%	40
D	0%	0%	2.3%	62.5%	35.2%	88
E	0%	0%	0%	0%	100.0%	15
Patients	84	28	24	94	55	285

[1]First AIS obtained within 7 days of injury: excludes cases with AIS unknown within 7 days of Injury

[2]AIS obtained 4 to 8 months post-injury

APPENDIX C

POLICY DESCRIPTION: Dissemination of Data – EXTERNAL

SCOPE: North American Clinical Trials Network (NACTN) PI's, administrators and clinical team members

PURPOSE:

To define who may have access to NACTN data for the purpose of data analysis and/or publication and to define the requirements and process for dissemination of data.

POLICY:

Executive Committee members will review and approve all proposals requesting access to NACTN data.

PROCEDURE:

For the purpose of this procedure, internal is defined as all members and former members of NACTN and their designees as approved by the PIs. External is defined as anyone not associated with NACTN.

External applicants requesting data from the database shall submit a standardized form available from the host site data manager. External applicants will submit a data request form which includes:

- a 500 word abstract which describes the purpose, specific aims, hypotheses, relevant evidence and relevance to the NACTN mission
- Identification of the data to be extracted from the database using the appropriate ITW form numbers
- Demonstration of the applicant's qualifications to complete the analysis (such as a current curriculum vitae/resume or NIH biosketch)
- Signed statement assuring:
  - accuracy of provided information on the form
  - agreement that data will be released solely to the requestor
  - compliance with home institution IRB policies
  - compliance with waiver statement

External applicants may not request NACTN data that is 3 years old or less unless provisions are made by NACTN's Executive Committee.

Approval or disapproval of the request must be by majority of all NACTN Executive Committee members. The decision may be based on the following criteria:

- Soundness of the scientific theory
- Redundancy of requests
- Relevance to the NACTN mission
- Availability and accuracy of data

If the request is denied by a majority of Executive Committee members, a member of the Data Integrity and Dissemination Oversight Committee (DIDO) will prepare a letter to the applicant explaining the reason for denial. The letter will be provided to the NACTN database manager for distribution to the applicant.

If the Executive Committee members approve the request, the form is sent to the database manager who will perform additional integrity checks on the data.

The disseminated data integrity checks:

- Disseminated data must be extracted a minimum of two times from the site of origin to assure any corrections made to the data are reflected in the dissemination.
- Disseminated data must go though the Data Reduction to Ensure Data Integrity procedure above which checks the data against possible errors listed in the data integrity manual.
- Any data points which remain in error are removed from the dissemination.
- The DIDO committee will oversee the integrity of disseminations.

Once the approvals and integrity checks are complete, the database manager will query the de-identified data and forward it solely to the requestor in the requested format. The database manager will notify the NACTN PIs and Executive Committee of the data dissemination. If DIDO determines that the data quality is insufficient for release (i.e. missing data, high incidence of errors), the database manager will notify the requestor and NACTN PIs as well as the Executive Committee. All PIs will be notified of the data request denial during the monthly conference call. Release of approved data or denial of requests must be completed in a timely manner.

External requestors will be charged a nominal fee, as determined by the Executive Committee, to cover expenses. Any questions from external requestors about this data, further clarifications or requests for additional data should be directed to the DIDO committee.

Data management will keep a record of what data have been released, to whom, and when. This information must be available for review by members of NACTN, and should be disseminated annually.

All request forms will be entered into a database that can be searched by request to the NACTN database manager.

Video distributed in professional presentations and publications to demonstrate NACTN procedures will fall under the data dissemination policy. Video of NACTN patients or procedures distributed for the press will fall under the Media Services & Public Relations Policy.

REFERENCES:	
EFFECTIVE DATE: January 2013	**APPROVAL DATE: January 14, 2013**
APPROVED BY: Executive Committee	**REPLACES POLICY DATED:**

APPENDIX D

Spine Injuries Sustained by US Military Personnel in Combat Are Different From Non-Combat Related Spine Injuries

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INTRODUCTION

Advancements in body armor and care at the point of injury are allowing American service members to return from the conflicts in Iraq and Afghanistan with previously "non-survivable" wounds[1]. Bony spine and spinal cord injuries (SCI) are more prevalent among Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) veterans than among veterans of previous conflicts[2,3], and combat-related spine differ from non-combat related SCI in multiple ways[2]. Estimates of mechanisms of SCI sustained in theater attribute 56% to 67% of SCI to explosive blasts[2-4], 15% to gunshot wounds[2,3], and 29% to motor vehicle accidents[2]. However, many combat-related spine injuries are part of a complex polytraumatic constellation of wounds, and there is also great heterogeneity in the injuries sustained by individuals from any given mechanism or combination of mechanisms[2,5-8].

The purpose of the present investigation was to characterize the context of spine injuries sustained by US military personnel in theater, and to analyze the association of the mechanisms of spine injuries with injury characteristics and clinical outcomes, in order to provide a basis for future controlled clinical studies. The authors sought to analyze potential relationships between mechanism of injury (blast, firearm, motor vehicle, other); the context of injury (battle or non-battle); type of injury (penetrating or blunt); anatomical level of injury (cervical, thoracic, lumbar); associated injuries; length of hospital stay, ventilator time, intensive care time; disposition including death.

METHODS

Study Design

This analysis is a retrospective cohort study of all US military personnel who sustained a bony spine or spinal cord injury while deployed in support of OEF or OIF between 1 January 2003 and 23 March 2008. This study also includes a nested case-control analysis of the injuries sustained by the service members included in this cohort. The study was conducted in accordance with a protocol approved by the Walter Reed National Military Medical Center (WRNMMC) Institutional Review Board, and comprises a military-specific component of the North American Clinical Trials Network (NACTN) for the Treatment of Spinal Cord Injury[9].

Records of service members who sustained a spine injury during the study period were extracted from the Joint Theater Trauma System (JTTS)[10,11], and matched to the records of patients admitted to WRAMC/WRNMMC.

Study Population

All US military personnel who sustained an SCI while deployed in support of OEF or OIF, and who were subsequently evacuated to a higher echelon of care between 1 January 2003 and 23 March 2008 were considered for inclusion in the study data set. To be included in the study, patients must have been active duty military service members age 18 years old or older, with an initial traumatic SCI and neurological deficit, but with a Glasgow Coma Scale (GCS) $\geq$ 12 in order to provide informed consent for inclusion in the study.

Measures

Continuous clinical variables such as vital signs recorded at the lowest echelon of care following injury, and military-, and injury-relevant, demographic variables were included in extracts from the JTTR. Continuous time-dependent variables were extrapolated from injury dates recorded in the JTTR, as well as WRAMC/WRNMMC records. Injury context (e.g. battle versus non-battle) and mechanism (e.g. blast versus motor vehicle accident) are also included in the JTTR, and were included in extracts used to create the final study data set.

The anatomic locations, types (e.g. blunt or penetrating), and severity of injuries were recorded using the Abbreviated Injury Scale (AIS)[12] and the overall severity of injuries was recorded using the Injury Severity Score (ISS)[13]. The AIS is a seven-digit, anatomically-based system for coding of injury location, tissue types involved, and severity of injury[12]. The investigators utilized this code to estimate the location, and severity of SCI, and, as a comparator to the Injury Severity Score.

The ISS is another anatomical injury scoring system that summarizes AIS scores for multiple injuries, thus reflecting the severity of multisystem, polytraumatic injuries. In the present investigation, ISS was classified into mild (1-15), moderate (16-25), severe (26-50), and critical (51-75)[13].

Analysis

Data were combined into a single de-identified limited data set for analysis. Records were reviewed for completeness and examined for trends in missing data. Chi squared tests were used to assess any statistically significant relations between data quality and time (data not shown).

The main exposures of interest were SCI caused by explosive blast (versus other mechanisms), injury type (i.e. blunt, penetrating, other), and the context in which the SCI occurred (i.e. in combat, in a motor vehicle accident, during athletic competition, etc.). The main outcomes of interest included severity of SCI and overall severity of injuries; time spent in intensive care; days spent on a ventilator; and total time spent in the hospital. These continuous time-dependent variables were log-transformed to more closely approximate a normal distribution. Militarily-relevant covariates including age, sex, military service (i.e. Army, Navy, Air Force, Marine Corps), theater of operations (i.e. Iraq or Afghanistan), time spent in transport between theater of operations and higher echelons of care, and year were analyzed with respect to the main exposures and outcomes of interest using χ^2 tests to detect any significant associations.

Fisher's exact test was used to compare demographic, SCI level, severity, mechanism, and dominant injury type with injury context. Two-sample t-tests were performed to analyze associations between SCI context, mechanism, dominant injury type, and severity with the duration of time subsequently spent hospitalized, in an intensive care unit (ICU), or on a mechanical ventilator. These time variables were log-transformed to more closely approximate a

normal-distribution. Factorial analysis of variance (ANOVA) was performed to further model the association of injury year, context, mechanism of injury, injury type, injury level, and ISS category with length of time outcomes. Log-times were analyzed in the two sample t-tests and the factorial ANOVAs. Lastly, univariate regression models were used to estimate the relative risk of injured service members returning to duty, being hospitalized, or dying by the same predictors enumerated above. Individuals were classified as returning to duty, being hospitalized, or being deceased based on the last available information available in the data set.

Assuming that 50% of service members included in the study population would be shown to have sustained an SCI as the result of a blast injury, a study population of 258 was estimated to be adequate to detect an absolute risk difference of 0.2 (risk ratio = 1.5) with 90% power and a type I error rate of α=0.5 (two sided) for dichotomous (i.e. χ^2 test) outcomes. Similarly, a sample size of 283 was estimated to be adequate to detect a 10% difference in continuous outcome variables between study groups, with 80% power and a type I error rate of α=0.5 and a mean of 1.5 ± 0.9 in the referent group.

The threshold level of statistical significance was set at a 5% probability of committing a Type I error (α), or $p < 0.05$. All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

The initial cohort included 307 individuals; 11 (3.6%) were excluded from analyses because of insufficient or missing data. Table 1 presents the demographic features of the study population and the context of injury, battle or non-battle. The final study population was comprised predominantly of males in the US Army, with an average age of 26.8 years. The average age of injured service members was similar between those injured in battle and those whose spine injuries occurred in a non-battle context. Similarly, the gender distribution and Service-affiliation was similar between battle and non-battle injuries. The majority of all spinal cord injuries occurred in the OIF theater of operations, but non-battle injuries were more likely to be sustained in the OEF theater of operations.

The cervical spine (C-spine) was the most commonly injured level, and this distribution was similar between the battle and non-battle context. Lumbar spine (L-spine) injuries were more likely to occur in battle (61.7% vs. 42.2%; $p = 0.002$). Blast was the most frequent mechanism of all SCI included in this population (42.2%), and all blast injuries occurred in battle. The most frequently recorded International Severity Scores (ISS) were in the Severe range (37.2%), and these ranges were recorded more frequently for SCI that occurred in battle (44.7%) than non-battle (20%; $p < 0.001$). Battle-related SCI were also more likely to be classified as Critical than were non-battle SCI (13.6% vs. 5.6%), and this association was statistically significant ($p = 0.458$). Notably, Mild range ISS occurred more frequently among non-battle SCI (52.2%) than battle-related SCI (20.9%; $p < 0.001$).

The most common injury type recorded was blunt SCI (67.9%), though this distribution also varied according to injury context: 96.7% of non-battle SCI were blunt, versus 55.3% of battle related SCI ($p < 0.001$). Penetrating injuries however, were more common in the context of battle (42.7% vs. 3.3%; $p < 0.001$).

Figure 1 displays the annual cumulative incidence of spine injuries for the study period. While the total number of spine injuries increased throughout the study period, the proportion of

injuries sustained in battle increased. Battle-related injuries began to outpace non-battle SCI in 2006, and the greatest cumulative incidence of spine injuries was observed in 2007.

Table 1A presents the distribution of spinal injuries by level, according to the context in which the injuries were sustained. Injuries at all levels were more common in battle, and this difference was statistically significant (χ^2 (6df) = 17.2, p = 0.0086), but the relative proportions are more disparate for injuries affecting more than one spinal level. Of the 38 injuries affecting the C-, and L-spine only, 32 (84.2%) occurred in battle, whereas only 6 (15.8%) occurred in a non-battle setting. Similarly, injuries of the T-, and L-spine were more common in battle than in a non-battle setting (77.8% vs. 22.2%, respectively).

Table 2 presents the mechanism of spine injury, analyzed according to the context in which it occurred (battle vs. non-battle) and dominant injury type (blunt vs. penetrating). A total of 4 patients were classified as having spine injury due to thermal injury, and all of these were also associated with blast injuries sustained in battle, so are included in that group for this analysis. The majority of gunshot wound-related injuries (98.5%) were classified as penetrating, and occurred in battle (95.6%). SCI classified as being due to "other" mechanisms (21.2%) includes injuries that occurred from falls, from machinery, sports injuries, and injuries for which no cause was listed in the initial data set, and most of these injuries occurred in a non-battle setting, and were blunt in nature (85.5%). The majority of blast injuries (81%) were classified as blunt. The single individual whose spine injury is classified as a blunt injury from a gunshot wound sustained in battle was noted to have sustained a T-spine injury not otherwise specified (AIS: 620099; ICD-9: 952.10).

Table 3 presents Abbreviated Injury Scale (AIS) severity scores of spine injuries that occurred in battle and were classified as blunt were compared to those whose injuries that occurred in a non-battle context (total n = 204). More than twice as many non-battle C-spine injuries (17%) as non-penetrating battle injuries (7.3%) were classified as Critical, but this difference was not statistically significant. This trend was reversed for L-spine injuries, with 12.1% of non-penetrating battle spinal injuries and 5.3% of non-battle spinal injuries being classified as Serious. The majority of injuries at each level were non-penetrating, battle-associated injuries, and this disparity is most notable for L-spine injuries (68.6% vs. 31.4%).

Table 4 presents the duration of hospital stay, time spent on a ventilator, and time spent in an intensive care unit (ICU) in days with respect to year of injury, military operation, injury context, dominant injury type, mechanism, injury level, and ISS category. A total of 282 patients were listed has having been hospitalized after their spine injury, 190 spent time in an ICU, and 133 were placed on a mechanical ventilator. The mean length of hospital stay was 11.5 days (range: 2-130 days), the mean length of ICU stay was 7.3 days (range: 2-75 days), and the mean time spent on a ventilator was 7.4 days (range: 2-75 days; data not shown).

There was a statistically significant decrease in the mean time spent in the hospital between the beginning of the study period and the end of 2007, the last full year analyzed (11.17 vs. 5.69 days; F = 9.77, p < 0.001), and similar trends were observed for mean ICU time (5.11 vs. 4.07 days; F= 3.82, p = 0.0052) and mean ventilator time (5.28 vs. 4.09 days; F = 3.36, p = 0.0118). However, for each clinical outcome, the lengths of time were generally longer in the intervening years (2004-2006) than both 2003 and 2007.

Two sample t-tests indicated that patients who sustained spine injury in battle had longer

hospital stays (11.41 vs. 7.95 days; $p = 0.0136$), and longer ICU stays (6.2 vs. 4.33 days; $p = 0.031$) than those who sustained an SCI outside of battle, but neither association was significant when examined with factorial ANOVA. No statistical associations were observed for penetrating injuries when compared to blunt injuries, or among different SCI levels.

Severity of injuries, as indicated by ISS category, was strongly associated with length of hospital stay ($F = 9.29$, $p < 0.0001$), time spent in an ICU ($F = 10.95$, $p < 0.0001$), and time spent on a ventilator ($F = 8.1$, $p < 0.0001$). Mild category ISS was associated with the shortest lengths of time, and Critical category scores being associated with the longest lengths of time.

Table 5 presents the association of year of injury, military operation, injury context, dominant injury type, mechanism, injury level, and ISS category with last known disposition: returned to duty, hospitalized, or deceased. All presented relative risks (RR) are univariate models that compare the level of the variable in question to all other levels of that variable. Multivariate models failed to converge. Individuals who sustained blunt injuries were more likely to return to duty than individuals who sustained penetrating injuries (RR = 8.9, 95% CI: 1.12-65.15), as were individuals who sustained isolated C-spine injuries (RR = 3.5, 95% CI: 1.56-7.86), and those who sustained spine injuries in motor vehicle crashes (RR = 2.5, 95% CI: 1.02-6.04). Individuals with ISS scores categorized as mild were more likely to return to duty (RR = 21.7, 95% CI: 5.17-91.4).

Individuals' final disposition was classified as hospitalized (n=265, 89.5% of total) if the latest available data indicated that they were discharged to a treatment facility in theater (8; 3% of hospitalized patients), Landstuhl Regional Medical Center (LRMC) (17; 6.4%), a military treatment facility in the United States (117; 44.2%), a Veterans Affairs hospital (67: 25.3%), a civilian hospital (21; 7.9%), or placed in a medical hold status (35; 13.2%). Those individuals who sustained both C-spine and T-spine injuries were more likely to be hospitalized than those who had injuries at other spinal levels (RR = 1.1, 95% CI: 1.02-1.17), as were those whose injuries were ISS category moderate (RR = 1.11, 95% CI: 1.04-1.18). Those with ISS category mild injuries were less likely to have a final disposition to a hospital than other categories of ISS (RR = 0.84, 95% CI: 0.75 – 0.94).

A total of 10 individuals in this study population died of their injuries, making the overall case fatality rate 3.38%. The only statistically significant increased risk was among those with injuries classified as critical (RR = 5.31, 95% CI: 1.58-17.86). Of note however, 100% of fatalities occurred in battle, and 7 of 10 were due to blast injuries; the remaining 3 were due to gunshot wounds.

DISCUSSION

This study sought to retrospectively characterize the possible association between battle and non-battle spinal cord injuries with mechanisms of injury, and injury type by analyzing a cohort of US military personnel who sustained a spinal cord injury while deployed in support of OIF or OEF. The study population largely reflected the known demographics of the active duty US military, and was comprised predominantly of males in their mid-twenties. The military Service affiliations recorded also reflect the composition of the forces deployed in support of the missions in Iraq and Afghanistan, with the US Army and US Marine Corps as the primary forces.

In general, battle associated spinal injuries were more likely to involve multiple spinal levels, especially the Lumbar spine, to be penetrating in nature, and to have been caused by blasts or gunshot wounds. There was a trend toward greater severity and longer hospital and

ICU stays among battle-associated spine injuries, but this association was not always statistically significant.

As in previous studies, the majority of bony spine and spinal cord injuries were caused by blasts and gunshot wounds, though the proportions of those two mechanisms are different from previously published estimates, with blast injury contributing relatively fewer injuries (42.2% vs. 65-67%) and gunshot wounds contributing relatively more (23% vs. 15%)[3,14]. Penetrating spinal cord injuries occurred almost exclusively in battle, but blunt injuries were more evenly distributed between the combat and non-combat setting. While it is not unexpected that battle-associated SCI mechanisms were primarily blast and gunshot wounds, it is notable that the vast majority of blast injuries were blunt, not penetrating. One possible explanation is that blunt SCI caused by blasts affected service members mounted in vehicles that provided partial protection from the forces of explosions, and from penetrating injury from objects that became projectiles because of the explosions.

The findings that battle-associated spine injuries are classified by the International Severity Score as Severe or Critical, and that these patients had somewhat longer, more intensive hospital courses may indicate that these patients sustained multi-systemic, polytraumatic injuries, of which spine injury comprised only a component. This explanation is supported by the finding that Abbreviated Injury Scale classifications were distributed similarly between non-penetrating, battle injuries and non-battle injuries.

The finding that multilevel injuries are more common among the combat-injured could indicate a unique type of spine injury, caused by the translation of explosive energy through a vehicle and into seated service members' pelvic girdle, sacrum, and lumbar spine, or by vehicle roll-overs that occur secondary to attacks by improvised explosive devices. This low lumbar and thoracolumbar burst mechanism of spine injury was described as early as 2011[15], and subsequently noted to be a very common type of spine injury sustained in combat[2,6,14,15]. Freedman et al., later noted though, that the incidence of thoracolumbar burst fractures increased from 0.63 per 100 LRMC trauma admissions in 2007-2008 to 3.0 per 100 LRMC trauma admissions in 2009-2010, the time period immediately following that of the present investigation, while the incidence of complete spinal cord injury decreased over time, from 66.7%-28.5%, though this association was not statistically significant ($p = 0.25$)[14]. This inverse association over time might also explain in part the decreasing length of hospital and ICU stay, and decreasing time spent on a mechanical ventilator described above.

Further studies correlating the pathoanatomic features of the spinal injuries sustained by service members in this cohort with injury mechanisms and types of exposures are needed to fully characterize the risks of spine injury in specific patient groups and various tactical situations, and to differentiate blunt spine injury sustained in battle from ostensibly similar blunt injuries sustained in motor vehicle crashes.

The association between battle injury and mortality, length of hospital stay, time spent in the ICU and time spent on a ventilator, may support the hypothesis that battle-related spine injuries are components of multisystem polytraumas. In a case series by Lehman et al. describing low lumbar and thoracolumbar burst fractures, none of the 32 patients studied had isolated spinal injuries; rather 40.6% had open extremity fractures, 25% had penetrating abdominal wounds, 12.5% had traumatic amputations, and 31% had pulmonary trauma[15].

It is intriguing though that there is a negative association between the length and intensity of hospital course and the year in which a patient sustained a spine injury, and that this association was statistically significant. Possible explanations for this include improved military

tactics, equipment, or personal protective equipment that shifted injuries away from the more severe end of the spectrum (i.e. primary prevention measures); refined point of injury care delivered by combat medics and corpsmen that stabilized patients, and thereby mitigated negative sequelae early in their clinical course; improved medical evacuation practices; or, improved neurosurgical, medical, and rehabilitative care of patients with traumatic spinal cord injuries. The underlying reasons for the shortened hospital courses of spine-injured patients are likely multifactorial, and the elucidation of their relative contributions to this presumably improved clinical course is an important area for future research.

Strengths of this investigation include a relatively robust sample size, which provided adequate power to detect smaller than those observed, and the fact that leveraging the Joint Theater Trauma Registry enabled classification of spine injuries by context, type, and mechanism at a point more proximal to the actual injury than would have been possible if such associations were attempted retrospectively, once patients had returned to the United States, and recovered adequately enough to meet criteria to provide informed consent.

This study also has several limitations, including variable recording of vital signs at the lowest echelon of care. Some of these vital signs may have been found to be predictors of patients' clinical course in the present study. However, because of the setting in which these vital signs were recorded – that is, often austere environments in which providers are treating multiple casualties, or mass casualty events – the investigators found that vital signs were recorded sporadically, and that there was a statistically significant association between the presence of such clinical data and the injury exposures of interest. To avoid a potential confounder, these data were therefore not included in analyses.

The variable recording of clinically relevant physiologic data also called into question the reliability of some spine injury classifications, such as cord contusions versus lacerations; fractures with versus without cord involvement, and others. Again, to avoid potential confounders, these data were not included in the final analyses. Future studies will attempt to answer the questions stated above, and such investigations will provide additional detail regarding the reliability and accuracy of the spine injury characteristics recorded in the theater of operations.

Finally, several of the outcomes of interest, namely return to duty and mortality, were observed in small numbers of individuals in the study population. This limited the authors' ability to conduct robust analyses of the prognostic value of variables such as context in which injury occurred, type of injury, and injury level. While statistical significance may not have been observed for some of these associations, several trends emerge that should be investigated further in future studies of combat related spine injuries

The present study provides evidence that blunt spinal injuries sustained in battle as a result of explosive blasts are more severe, and follow a different clinical course than non-battle blunt spinal injuries. Further characterization of the natural history of such blast-, and combat-related injuries will be useful in planning and targeting therapies to injured service members, and in providing information that can be used for the development of novel therapeutic interventions. Comparison of blast, and combat-related spine injuries to civilian spinal trauma may also help elucidate salient similarities and differences in spine, and multisystem trauma pathophysiology and recovery. Most importantly though, detailed description of the pathoanatomic features of the injuries sustained by service members studied in this project promises to yield insights into the continuing evolution of surgical care of spine injured patients, the identification of specific risk

groups, and definition of prognostic factors that can in turn be used as the basis for improved spine injury treatment algorithms.

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APPENDIX E

Spinal Cord (2015), 1–8

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ORIGINAL ARTICLE

Rationale, design and critical end points for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): a randomized, double-blinded, placebo-controlled parallel multi-center trial

MG Fehlings[1], H Nakashima[1,2], N Nagoshi[1,3], DSL Chow[4], RG Grossman[5] and B Kopjar[6]

Background: Riluzole is a sodium channel-blocking agent used in treating amyotrophic lateral sclerosis. It has been approved by the U.S. Food and Drug Administration, Canadian and Australian authorities, and in many other countries. A phase I trial of riluzole for acute spinal cord injury (SCI) provided safety and pharmacokinetic data and suggested neuroprotective benefits. A phase IIB/III double-blinded randomized controlled trial (RCT) started in January 2014 (https://clinicaltrials.gov, NCT01597518). This article describes the pathophysiological rationale, preclinical experience and design of the phase IIB/III RCT of Riluzole in Acute Spinal Cord Injury Study (RISCIS).

Objectives: The primary objective of the trial is to evaluate the superiority of riluzole, at a dose of 100 mg BID in the first 24 h followed by 50 mg BID for the following 13 days post injury, compared with placebo in improving neurological motor outcomes in patients with C4–C8 level, International Standards for Neurological Classification of Spinal Cord Injury Examination (ISNCSCI) grade A, B or C acute (within 12 h post injury) SCI.

Setting: Acute trauma centers worldwide

Methods: A double-blind, multi-center, placebo-controlled RCT will enroll 351 participants randomized 1:1 to riluzole and placebo. The primary end point is the change between 180 days and baseline in ISNCSCI Motor Score. This study has 90% power to demonstrate nine points difference in the ISNCSCI Motor Score at one-sided $\alpha = 0.025$.

Results: Currently enrolling in 11 centers.

Conclusion: This study will provide class I evidence regarding the safety and neuroprotective efficacy of riluzole in patients with acute cervical SCI.

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INTRODUCTION

Background and rationale

Spinal cord injury (SCI) is a devastating event resulting in severe neurological deficit, loss of function and deterioration in quality of life. The annual incidence is 15–40 cases per million, and there are more than one million people living with SCI in North America.[1] The annual cost of SCI in North America exceeds seven billion dollars,[1] and the impact is immense at a personal, family and societal level.

During the last decade, a number of therapies have been investigated in clinical trials bringing new hope to patients with SCI.[2] However, effective therapies, shown to improve neurological and functional recovery, remain absent.

Riluzole is a benzothiazole anticonvulsant drug that is approved for use in amyotrophic lateral sclerosis (ALS) by the U.S. Food and Drug Administration (FDA) and by the regulatory authorities in numerous other countries and jurisdictions.[3] Riluzole modulates excitatory neurotransmission, and the neuroprotective mechanisms have been shown to improve survival in the setting of ALS.[3] Preclinical studies of riluzole in the setting of SCI have also demonstrated functional recovery by preventing the aberrant release of sodium and glutamate imbalance.[4,5] As such, riluzole is an appealing agent for translation into clinical trials for SCI because of its well-defined human safety record over the past two decades in the treatment of ALS.

A phase I clinical trial investigating the safety and pharmacokinetics of Riluzole in acute SCI was completed in 2011 (https://clinicaltrials.gov no. NCT00876889),[6] and motor scores were seen to improve for riluzole-treated cervical injury patients on the International Standards for Neurological Classification of Spinal Cord Injury Examination (ISNCSCI), compared with a nonconcurrent comparison group treated with standard of care. A phase IIB/III randomized multi-center controlled trial evaluating the efficacy and safety of riluzole in the management of patients with acute SCI entitled the Riluzole in Acute Spinal Cord Injury Study (RISCIS) commenced in January 2014 (https://clinicaltrials.gov, registration number NCT01597518). The completion of the RISCIS study will provide level 1 evidence either confirming or refuting efficacy of riluzole in the treatment of acute SCI.

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Pathobiology of SCI. The pathobiology of acute SCI involves a primary mechanical injury followed by the secondary injury resulting in further damage. The primary injury involves an array of complex biomechanical forces including acute contusion, compression or laceration due to displacement of bone or disc, and shear stresses loaded on axons or blood vessels. This primary event initiates a post-lesion signaling cascade of downstream events, known as the secondary injury. Petechial hemorrhage in the gray matter and edema in the white matter occur, and thrombosis and vasospasm in microvasculature lead to ischemia of neuronal tissues.[7] The ischemia leads to neuronal membrane dysfunction, which includes the abnormal continuous activation of neuronal voltage-dependent sodium channels (Figure 1).[7] This activation causes an increase in intracellular sodium levels. The combination of events following the influx of sodium ions leads to regional cell death, and is the main pathogenesis of secondary neural injury. This mechanism of secondary injury provides the rationale for the use of a sodium channel-blocking agent to reduce the extent of injury.

An intervention to mitigate damage caused by the primary injury in SCI is unlikely; however, the opportunity to preserve remaining viable neurological tissue by mitigating the evolution of secondary injury could result in improved post-injury outcomes.

Treatments for SCI. Clinical guidelines for the management of SCI emphasize the need for decompression of the spinal cord, restoration of spinal stability and cardiopulmonary and metabolic support. Currently, there are few therapeutic treatments demonstrating functional outcome improvement in human SCI. Clinical trials with methylprednisolone (NASCIS II and III)[8] and GM-1 ganglioside[9] have been performed without strong positive results. A recent prospective, multi-center study suggests that early decompression within the first 24 h post injury is associated with better neurological outcomes than later surgery.[10]

Evidence for use of riluzole in SCI. Riluzole is a sodium channel-blocking benzothiazole anticonvulsant.[3] SCI results in a deleterious accumulation of intracellular sodium level ([Na+]i) through voltage-gated Na+ channels within neural axons,[11] and dysfunction of membrane-bound Na+–K+-ATPase pump with a reduction in Na+ efflux.[12] The resulting membrane depolarization associated with cellular inability to remove [Na+]i favors further Na+ influx via the Na+ channels. The marked increase [Na+]i leads to an influx of Ca2+ through Na+–Ca2+ exchange pump. This Ca2+overload stimulates a variety of Ca2+-dependent enzyme systems such as calpains and phospholipases, leading to structural and functional injury.[13] The neuroprotective effects of riluzole appear to result from a blockade of sodium channels, and prevention of exaggerated Ca2+ influx (Figure 1).[14] In addition, riluzole has a role as an anti-glutamatergic agent via the inhibition of glutamate release, the prevention of glutamate receptor hypofunction and the increase of glutamate uptake by activating glutamate transporters.[15,16] The multifaceted effects of riluzole on excitotoxicity and neuromodulation make it a promising neuroprotective treatment option after SCI. Dr Fehlings' group confirmed the effect of riluzole in SCI using a cervical injury model in rats by comparing other sodium channel blockers.[4] Functional neurological recovery was achieved only with riluzole, and significant long-term tissue sparing and a reduction of cavity area were observed.

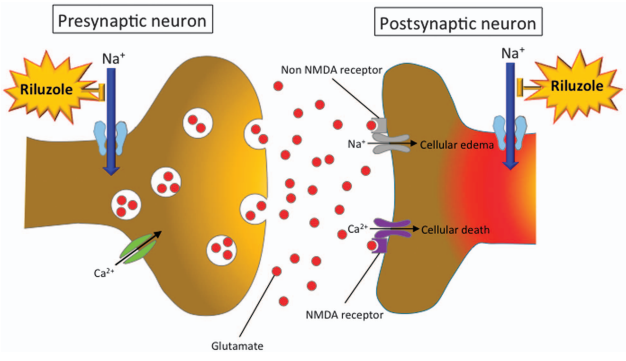

Figure 1 Schematic image of the primary mechanism by which riluzole attenuates the secondary injury in SCI. During the early stage of secondary injury, neuronal ionic balance is disrupted and the intracellular sodium concentration increases as a result of trauma-induced activation of voltage-sensitive sodium channels. The increase in intracellular sodium concentration also promotes concomitant influx of calcium ions, resulting in the development of intracellular acidosis. The excessive influx of sodium and calcium triggers pathologic extracellular release of excitatory neurotransmitter glutamate, leading to cytosolic edema and cellular death. Riluzole blocks the sodium channels in neurons and prevents the increase in intracellular sodium concentration, contributing to the inhibition of cellular death.

Optimal timing for administration of riluzole in SCI. The extracellular glutamate rises to a toxic level within 15 min after SCI in rats.[4] Dr Fehlings' group evaluated the timing of riluzole administration in rodents with severe cervical SCI, and demonstrated that the treatment initiated at 1 and 3 h post injury contributed to (1) sensory-motor function improvement, (2) improved axonal conduction and (3) reduced apoptosis and inflammation without increased neuropathic pain.[5] Extrapolating from these results, we estimated a therapeutic time window of 12 h post injury for riluzole in humans, given that the pathobiological changes in SCI peak approximately four times more rapidly in rats than they do in humans.[5]

The phase I clinical trial of riluzole in SCI. The phase I clinical trial was completed in 2011 (https://clinicaltrials.gov no. NCT00876889). Thirty-six patients (28 cervical and 8 thoracic) were enrolled at six clinical centers of the North American Clinical Trials Network (NACTN).[6] The patients enrolled were admitted within 12 h of SCI, and assessed using ISNCSCI as grade A, B or C at admission. Riluzole (50 mg) was administered every 12 h orally or by nasogastric tube, starting within 12 h of injury for 28 doses. A nonconcurrent comparison group was formed of 36 SCI patients who had received standard of care treatment without riluzole. There were no serious adverse effects or death. Increase in liver enzyme and bilirubin levels were found in 14–70% of patients, but these elevations returned to normal levels without serious events. With regard to other medical complications, the specific types of severe and moderate complications such as infection, pulmonary failure or hematological disease, occurred in both groups of patients, with no significant differences in occurrence rates between groups.

Significant ISNCSCI motor score improvement from admission to 90 days in cervical injury patients was observed in the riluzole-treated group. ISNCSCI grade B patients with cervical injury showed the greatest gains in this motor score. In patients with thoracic SCI, significant motor recovery was not observed because patient numbers were small and all had complete paralysis. In general, the ISNCSCI motor scores are not sensitive to segmental clinical recovery in the thoracic region. On the basis of these results, the phase IIB/III clinical trial for cervical acute SCI began in January 2014, and is known as RISCIS.

Clinical pharmacokinetics of riluzole in patients with SCI. To obtain information about the pharmacokinetics (PK) and pharmacodynamics (PD) of riluzole and relate that information to toxicity and efficacy outcomes, individual and population pharmacokinetics of enterally administered riluzole were characterized in a Phase I clinical trial.[17] The peak concentration and 12-h area under the plasma concentration curve $(AUC)_{(0–12h)}$ achieved in SCI patients were lower than those in ALS patients on the same dose basis, owing to a higher clearance and larger volume of distribution in SCI patients. The finding in SCI patients of large interpatient variability in plasma concentration and an increase in the clearance and distribution of riluzole between the 3rd and 14th days after SCI, with a lower plasma concentration of riluzole on the 14th day, stressed the importance of monitoring changes in drug metabolism after SCI in interpreting the safety and efficacy of therapeutic drugs that are used in clinical trials in SCI.

Objectives

The primary objective of the RISCIS study is to compare neurologic motor recovery at 6-month follow-up between adult patients with acute SCI receiving either riluzole or a placebo for the same duration after acute SCI. As secondary objectives, the impact of this riluzole regimen on sensory recovery, functional outcomes, quality of life outcomes, health utilities, as well as on mortality and adverse event rates will be evaluated. The study hypothesis is that subjects with acute SCI treated with riluzole will experience superior neurological, functional and quality of life outcomes, as assessed using established measures, at follow-up points to 12 months as compared with those receiving placebo.

Trial design

RISCIS is a randomized, double-blinded, multi-center, placebo-controlled, two-arm parallel group superiority trial with a sequential adaptive design.. This trial has been registered with https://clinicaltrials.gov (no. NCT01597518). The trial follows applicable institutional and governmental regulations concerning the involvement of human subjects in clinical research. The study Sponsor is AO North America Charitable Foundation and AOSpine North America Chi Lam Project Manager, AOSpine North America, Clam@aospine.org, a nonprofit foundation for excellence in spine.

MATERIALS AND METHODS

Study setting

The investigational sites are selected from the AOSpine North America Research Network, a clinical research consortium funded by AOSpine North America, and the North American Clinical Trials Network (NACTN) for Treatment of Spinal Cord Injury sponsored by the Christopher Reeve Foundation and supported by the U. S. Department of Defense. It is planned, pending funding, that additional sites worldwide will join the study. The central trial management center is at the AOSpine Methods Core where the central electronic online data capture system is held. Dr Michael G Fehlings is the Principal Investigator and chairs the trial Steering Committee and Dr Robert G Grossman is the Co-Principal Investigator. The trial Steering Committee also consists of several content experts, a pharmacologist and a statistician. The consortium centers are listed in Table 1. All treatment sites are primary care research hospitals and clinics. Currently, 14 sites are in the United States, two are in Australia and one is in Canada. At each of these sites, there is a designated primary site investigator supported by at least one professional study coordinator, who is responsible for day-to-day operations. Before commencing enrollment, all sites received research ethics board approval and training in study operations by the AOSpine Methods Core.

Table 1 Summary of centers participating in the RISCIS Study

Principal investigator	*Site*
Nicholas Theodore, MD	Barrow Neurological Institute, Phoenix, AZ, USA
Paul Arnold, MD	Kansas University Medical Center, Kansas City, KS, USA
Ahmad Nassr, MD	Mayo Clinic, Rochester, MN, USA
James Schuster, MD	Hospital of the University of Pennsylvania, Philadelphia, PA, USA
James Harrop, MD	Rothman Institute, Philadelphia, PA, USA
Darrel Brodke, MD	University of Utah, Salt Lake City, UT, USA
Christopher Shaffrey, MD	University of Virginia, Charlottesville, VA, USA
Bizhan Aarabi, MD	University of Maryland, Baltimore, MA, USA
Michele Johnson, MD	University of Texas Health Science Center, Houston, TX, USA
Maxwell Boakye, MD	University of Louisville, Louisville, KY, USA
James Guest, MD	University of Miami, Miami, FL, USA
Joseph Hobbs, MD	Brooke Army Medical Center, Fort Sam Houston, TX, USA
Graham Creasey, MD	Stanford University, Stanford, CA, USA
Ralph Stanford, MD	Prince of Wales Hospital, Sydney, NSW, Australia
Jonathon Ball, MD	Royal North Shore Hospital, Sydney, NSW, Australia
Robert Grossman, MD	Houston Methodist Hospital-NACTN Coordinating Center, Houston, TX, USA
Michael Fehlings, MD, PhD	University of Toronto Spine Program and Toronto Western Hospital, Toronto, ON, Canada

Abbreviations: AZ, Arizona; CA, California; FL, Florida; KS, Kansas; KY, Kentucky; MA, Massachusetts; MN, Minnesota; NSW, New South Wales; ON, Ontario; PA, Pennsylvania; TX, Texas; UT, Utah; VA, Virginia.

Eligibility criteria

Detailed inclusion and exclusion criteria are provided in Table 2.

Main inclusion criteria

1. SCI with ISNCSCI Impairment Scale Grade 'A,' 'B' or 'C' and neurological level of injury between C4 and C8 based upon the first ISNCSCI evaluation after arrival at the hospital.
2. Aged between 18 and 75 years.
3. Able to receive the investigational drug within 12 h of injury.

Key exclusion criteria

1. History of prior SCI.
2. Injury arising from penetrating mechanism.
3. Significant concomitant head injury defined by a Glasgow Coma Scale score <14 with a clinically significant abnormality on a head CT.
4. Evidence of hepatic or renal impairment.

Enrollment and randomization. Patients who satisfy the inclusion and exclusion criteria (Table 2), agree to study participation and sign the informed consent after being explained all risks and benefits associated with participation in the trial are enrolled and randomized at a ratio of 1:1 to riluzole or placebo arm (Figure 2). The randomization sequence is stratified by site and uses the randomly permuted block sizes of 2 and 4. The randomization sequence is generated by the biostatistician at the central trial management center. For each subject, randomization occurs by opening the lowest sequential number of the sealed randomization envelopes. Each envelope contains a unique number that corresponds to the number on a pre-stocked medication container containing either riluzole or placebo. Throughout randomization and follow-up, the

Table 2 Eligibility inclusion and exclusion criteria

Eligibility inclusion criteria	● Age between 18 and 75 years inclusive ● Able to cooperate in the completion of a standardized neurological examination by ISNCSCI standards (includes patients who are on a ventilator) ● Willing and able to comply with the study protocol ● Informed Consent Document (ICD) signed by patient, legal representative or witness ● Able to receive the investigational drug within 12 h of injury ● ISNCSCI Impairment Scale Grade 'A,' 'B' or 'C' based upon the first ISNCSCI evaluation after arrival to the hospital ● Neurological Level of Injury between C4 and C8 based upon first ISNCSCI evaluation after arrival to the hospital ● Women of childbearing potential must have a negative serum β-hCG pregnancy test or a negative urine pregnancy test
Eligibility exclusion criteria	● Injury arising from penetrating mechanism ● Significant concomitant head injury defined by a Glasgow Coma Scale score <14 with a clinically significant abnormality on a head CT (head CT required only for patients suspected to have a brain injury at the discretion of the investigator) ● Pre-existent neurologic or mental disorder which would preclude accurate evaluation and follow-up (i.e., Alzheimer's disease, Parkinson's disease, unstable psychiatric disorder with hallucinations and/or delusions or schizophrenia) ● Prior history of spinal cord injury ● Recent history (<1 year) of chemical substance dependency or significant psychosocial disturbance that may impact the outcome or study participation, in the opinion of the investigator ● Is a prisoner ● Participation in a clinical trial of another Investigational Drug or device within the past 30 days ● Hypersensitivity to riluzole or any of its components ● Neutropenia measured as ANC measured in cells per microliter of blood of <1500 at screening visit ● Creatinine level of >1.2 mg dl^{-1} in males or >1.1 mg dl^{-1} in females at screening visit ● Liver enzymes (ALT/SGPT or AST/SGOT) three times the ULN at screening visit ● Active liver disease or clinical jaundice ● Subject is currently using, and will continue to use for the next 14 days any of the following medications which are classified as CYP1A2 inhibitors or inducers:* Inhibitors: – Ciprofloxacin – Enoxacin – Fluvoxamine – Methoxsalen – Mexiletine – Oral contraceptives – Phenylpropanolamine – Thiabendazole – Zileuton Inducers: – Montelukast – Phenytoin *Note: no washout period required; if these medications are discontinued, subjects are eligible to be enrolled in the trial ● Acquired immune deficiency syndrome (AIDS) or AIDS-related complex ● Active malignancy or history of invasive malignancy within the last 5 years, with the exception of superficial basal cell carcinoma or squamous cell carcinoma of the skin that has been definitely treated. Patients with carcinoma *in situ* of the uterine cervix treated definitely more than 1 year before enrollment may enter the study ● Lactating at screening visit

Abbreviations: ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.

subjects, physicians and data collectors remain blind to treatment allocation. Emergency unblinding procedure for safety reasons is provided.

Withdrawal/discontinuation of subjects. A subject will be withdrawn from the study for any of the following reasons:

1. In rare cases, subject may be enrolled before receiving all screening laboratory tests. If the results show clinically significant abnormalities, the subject may be discontinued.
2. Subject voluntarily withdraws consent after enrollment and terminates participation.
3. The investigator withdraws the subject. If this decision is made for safety reasons or noncompliance with the study protocol or procedures, the sponsor/CRO will be notified immediately.
4. The investigator or the sponsor stops the study or stops the patient's participation for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and good clinical practice.

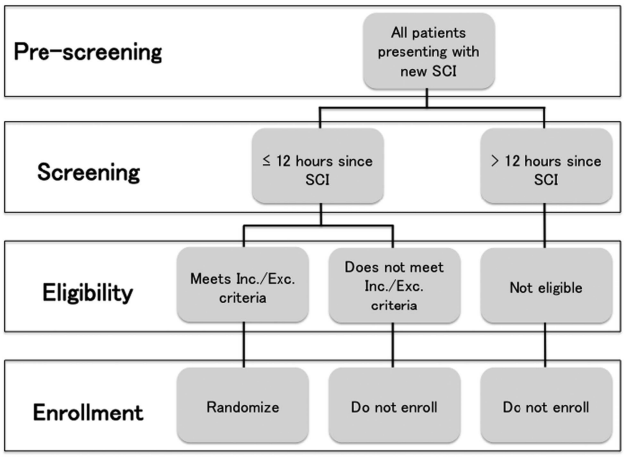

Figure 2 Screening and enrollment design.

For each case, detailed information will be obtained explaining circumstances leading to the withdrawal. This will be recorded on the Subject Withdrawal Form. Investigational drug assigned to the withdrawn subject shall not be assigned to another subject. The remaining study medication for the withdrawn subject will be obtained from the subject and kept at the site to be processed at the end of the study according to the disposal or return instructions.

For safety reasons, a subject who withdraws from the study for any reason before completion of the dose regimen and the last scheduled lab test will be assessed for safety evaluation purposes. This shall occur within 30 days of the last dose of the investigational drug.

Interventions: treatment description

Subjects assigned to the active treatment arm receive riluzole at a dose of 100 mg BID in the first 24 h followed by 50 mg BID for the following 13 days after injury. The decision to use the 100-mg loading dose was based on the pharmacokinetics/pharmacodynamics results in the Phase I study. This is an approved FDA dosage and the rationale is to get to optimal therapeutic levels faster. Subjects randomly assigned to the control arm receive a placebo capsule that is identical in shape, size and color to the riluzole capsule for the same duration and at the same interval. The drug is administered by a nurse daily, as it is prescribed and the medications are given to the patient by the nurse according to doctor's orders. There will be, therefore, a medical record of drug administration. External research monitors will perform on-site evaluations to ensure drug adherence (Complete Investigational Drug Log), and make sure that the data are accurate, reliable and complete and that the study was conducted in accordance to the protocol. In addition, there will be monitoring of riluzole plasma levels as in Table 4. At the time of randomization, enrolled subjects receive the medication containers containing the allotted quantity of riluzole or placebo tablets, accompanied with detailed instructions for use. Drug-related compliance is assessed and recorded throughout the study period. Surgical treatment including the approach (anterior or posterior), the type of operation (decompression, fusion or corpectomy) are left to the discretion of the treating surgeon. Postsurgical treatment, including the institution of rehabilitation measures, is left to the standard of care at the participating study site.

Outcome measures and follow-up

Primary efficacy outcome. The primary outcome is change in ISNCSCI total Motor Score (ISNCSCIMS) between baseline and 180 days after injury (Table 3). The ISNCSCI is a universal classification tool for SCI.[18] The time point of 180 days was chosen based on empirical evidence from an earlier study showing that the majority of functional change and recovery after SCI occurs by this time point.[6]

Table 3 Primary and secondary end points

Primary efficacy end point	● Absolute change in the International Standards for Neurological Classification of Spinal Cord Injury Examination (ISNCSCI) Total Motor Score (ISNCSCIMS) between 180 days and baseline
Secondary efficacy end points	● Change in ISNCSCI grade between baseline and 180 days. ● Spinal Cord Independence Measure (SCIM) III at 180 days.
Other end points	● Change in ISNCSCI Sensory Scores (Light Touch and Pin Prick) between 180 days and baseline ● Change in ISNCSCI Upper Extremity Motor Score between 180 days and baseline ● Change in ISNCSCI Lower Extremity Motor Score between 180 days and baseline ● Change in Short Form 36 Version 2 (SF-36v2) PCS, MCS and 8 dimensions between 180 days and pre-injury (recall) ● Change in EQ-5D health utility between 180 days and pre-injury (recall) ● Graded Redefined Assessment of Strength Sensibility and Prehension (GRASSP) at 14 days or Discharge (whichever occurs first) and 180 days ● Change in Numeric Pain Rating Scale (pain NRS) at 14 days, 84 days and 180 days

Secondary efficacy outcomes. The trial has two secondary efficacy outcomes.

- Change in ISNCSCI grade between baseline and 180 days
- Spinal Cord Independence Measure (SCIM) III at 180 days

The SCIM[19] is the only comprehensive rating scale that measures the ability of patients with spinal cord lesions to perform everyday tasks.

Other outcomes. Other outcomes consist of health-related quality of life SF-36 version 2, EQ-5D, Pain Numeric Rating Scale (Pain NRS), and sensorimotor upper limb function (Graded Redefined Assessment of Strength Sensibility and Prehension: GRASSP) outcomes (Table 4).[20]

Safety outcomes

All adverse events are recorded on an ongoing basis throughout the study period. All serious and unexpected adverse events will be reported to the Medical Monitor at the time of occurrence.

Pharmacological substudy

A subset of clinical centers, specifically nine NACTN centers, are the sites for the pharmacological substudy. It is assumed that a threshold level of blood plasma concentration of riluzole must be reached to achieve a therapeutic effect and that there is a therapeutic range of concentrations. The previously published reports of the pharmacology of riluzole in the Phase I trial reported large differences in maximal concentration of riluzole between patients. It is possible that the low levels of riluzole in some patients did not reach a threshold for efficacy. In grade B patients with cervical injuries, a positive correlation was found between the plasma concentrations and motor outcome scores when extreme peak concentration (C_{max}) values and motor scores were censored.[6] The pharmacological substudy aims to determine a safe and clinically effective therapeutic range of plasma concentration of riluzole. If

Table 4 Schedule of study activities

	Screening/ enrollment	*Surgery (if applicable)*	*72 ± 12 h post injury*	*7 ± 1 day post enrollment*	*14 ± 2 days*	*Discharge from acute care*	*84 ± 14 days*	*180 ± 30 days*	*365 ± 45 days*	*Unscheduled visit*
Sign ICD	×									
Health Information Release Form (if applicable)	×									
Inclusion/exclusion	×									
Obtain demographics	×									
Screening labs, PK plasma Clinical labs	×		×	×	×					
Pregnancy test (if applicable)	×		×		×		×	×	×	
ISNCSCI	×									
Randomization	×									
Dispense investigational drug	×									
Complete investigational drug log	×				×					
Medication compliance SW[a]	×				×					
Charlson Comorbidity Score	×									
Injury Severity Score	×									
SF-36v2.0	×[b]						×	×	×	
EQ-5D	×[b]						×	×	×	
Obtain and complete socio-economic and health behavior SWs	×									
Obtain and complete medical history SWs	×									
Spine trauma injury data SW	×									
Concomitant medications	×	×	×	×	×	×	×	×	×	×
Vital signs	×	×	×		×	×				
Record operative data		×								
MRI			×[c]							
SCIM III					×		×	×	×	
GRASSP					×[d]	×[d]		×		
Pain NRS					×		×	×	×	
Report AEs and SAEs (including intraoperative)		×	×	×	×	×	×	×	×	×
Discharge information						×				
Physical and occupational therapy						×	×	×	×	
Verify data and enter into eCRF within 48 h[e]	×	×	×	×	×	×	×	×	×	×

Abbreviations: AE, adverse event; eCRF, electronic case report form; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury Examination; MRI, magnetic resonance imaging; NRS, Numeric Rating Scale; SAE, serious adverse event; SCIM, Spinal Cord Independence Measure.
[a]Medication compliance should be completed daily.
[b]Recall of status before the injury.
[c]MRI between 48 and 72 hours at the discretion of the Investigator.
[d]GRASSP will be performed at 14 days or discharge (which occurs first).
[e]Data should be entered into the eCRF within 48 h, but no later than 14 calendar days from collection.

these can be established, monitoring riluzole plasma levels and adjustment of the enteral dose would be a rational approach to therapy.

The specific aims of the pharmacological substudy are to determine the individual peak and trough concentrations of riluzole after enteral administration of the study doses described above. From this, the aim is to derive individual pharmacokinetic parameters of half-life ($t_{1/2}$), systemic exposure ($AUC_{0\rightarrow 24}$), volume of distribution (V_d) and clearance by one-compartment model, using Bayesian iterative two-stage procedure. Riluzole concentration will also be correlated with laboratory measures including aspartate aminotransferase, alanine aminotransferase, white blood count and the incidence of adverse events, as well as with neurological outcome scores.

Participant timeline

Participant timeline is shown in Table 4.

Sample size, interim analysis and adaptive techniques

The statistical analysis will test the null hypothesis of the superiority of riluzole compared with placebo in change of ISNCSCIMS between the baseline and the 180-day follow-up (Δ ISNCSCIMS).

Statistical tests. The statistical testing of H_0 for the primary end point will be organized as a two-stage sequential adaptive design. There will be one interim

analysis at about 60% of the accrued sample in addition to the final analysis. The interim analysis has multiple functions:

Testing of H_0 (that is, efficacy)
Testing of H1 (that is, futility, lack of effect)
If none of the above, sample size will be adjusted, if indicated

The overall sequential design will be organized in the following way. The statistical design will address the efficacy and futility. The statistical testing of H_0 hypothesis will be performed as a one-way test with α level 0.025, testing the superiority of riluzole arm compared with placebo arm. The superiority of placebo over riluzole (that is, harmful effect of riluzole) will not be tested as it has no clinical implication. α-spending for the testing of H_0 will resemble an O'Brien–Fleming distribution. The testing for futility (H_1) will consequently be organized as one-way testing. The β-spending for futility testing will follow γ-distribution with the parameter (−1). The results of the interim analysis will be reviewed by the DSMB (Data Safety and Monitoring Board) and will not be shared with the sponsor, participating investigators or patients, except in the case that the study reaches termination or withdrawal criteria.

Sample size. On the basis of the above statistical design, specifications and empirically derived s.d. for ISNCSCIMS change of 24.08 from a large case series of prospectively followed SCI subjects in an earlier study, a sample size of 316 subjects (158 in each arm) will have 90% power to detect nine points difference in the Δ ISNCSCIMS at one-sided $\alpha = 0.025$. To account for losses to follow-up of up to 10%, the study will enroll 351 subjects.

The sample size estimate is based on certain assumptions. The main assumptions affecting the sample size are that of the true effect size and the s.d. for the difference in the Δ ISNCSCIMS. These assumptions will be verified during the study and sample size adjustment will be performed if needed, using the adaptive techniques. The sample size adjustment will be performed after the first interim analysis of the data.

Missing values. Any missing follow-up data will be imputed through a multiple imputation procedure that is less susceptible to bias than the complete case analysis technique. Multiple imputation is the preferred method for handling missing outcome data in therapeutic trials, as recommended by the FDA.

Study success. Study will be considered to successfully confirm the working hypothesis if H_0 for the primary end point has been rejected either at interim or the final analysis.

Secondary outcomes. Testing for all secondary outcomes will be based on appropriate statistical methods and two-way superiority testing. Secondary outcomes will not be tested at the interim analysis, except if the withdrawn rules were met.

Preplanned subgroup analysis. A preplanned subgroup analysis will compare the differences in Δ ISNCSCIMS among the subjects with ISNCSCI Impairment Scale Grade 'A,' 'B' and 'C.'

Safety. Safety will be monitored through the course of the study by a designated Safety Officer who is not associated with the Sponsor and is not an investigator in the study. Trends in serious adverse events, laboratory events and unexpected adverse events will be reviewed by external independent DSMB. The DSMB will evaluate safety information against the pre-specified safety stopping rules. The DSMB will also review the results of the interim statistical analysis.

Study population. The analysis will be performed on intention-to-treat population.

Quality assurance

Administration of study medication will be recorded in the Medication Compliance Log. External independent clinical research monitors will perform frequent on-site visits to ensure that the subjects have provided their consent to participate in the study, that the data are true, accurate, reliable and complete, that patient safety is maintained and that all adverse events are evaluated and reported, and that the study is conducted in accordance with the study protocol. Throughout the course of the trial, all subject-related source data will be transcribed into the eCRF online electronic data capture system OpenClinica (OpenClinica, LLC, Waltham, MA, USA), which will be maintained at the central trial management center. Study data in eCRF will be continuously monitored and any inconsistencies resolved through online ticketing system inbuilt into eCRF.

Publication policy

Trial data are owned by the Study Sponsor. Each investigator will obtain a copy of their site data set. A central data set will be maintained by the AOSpine Methods Core and will be used for all multi-center publications.

Subject insurance

Sponsor carries subject insurance in case of research-related injury.

Conclusion and current trial status

Preclinical studies suggest that glutamate-related excitotoxicity contributes to the pathology of SCI. Riluzole, an FDA-approved medication, has been shown to mitigate such excitotoxicity in animal models of traumatic spinal cord injury, leading to improved neurobehavioral outcomes. To investigate the efficacy and safety of riluzole in the treatment of human SCI, a multi-center, double-blinded, randomized controlled trial has been undertaken, and patients are being enrolled currently. At the time of writing, a total of 11 patients have been enrolled in the study.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

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Q4

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APPENDIX F

Confirmation

The 4th ISCoS AND ASIA JOINT SCIENTIFIC MEETING

14th–16th May 2015, Montreal, Canada

ISCOS The International Spinal Cord Society

ASIA American Spinal Injury Association

Step 1 Contact Details	Step 2 Abstract Details	Step 3 Authors Details	Step 4 Confirmation

Please check that all the information is correct before finishing the process.

Use the following credentials to login into the system if you need to edit your abstract submission details.

User:

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Contact Details

Title:	Dr.
Name:	MICHAEL
Surname:	FEHLINGS
Gender:	
Company / Institution:	University of Toronto
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Address:	
City:	
Country:	
Telephone:	

Presentation preference

Oral presentation

I. Abstract title

Efficacy & Safety Of Riluzole In Acute Spinal Cord Injury (SCI). Rationale & Design Of AOSpine Phase III Multicenter Double Blinded Randomized Trial

II. Abstract text

INTRODUCTION:. There is convincing evidence from the preclinical realm that the pharmacologic agent riluzole attenuates certain aspects of the secondary injury cascade leading to diminished neurological tissue destruction in animal SCI models. The safety and pharmacokinetic profile of riluzole have been studied in a multicenter pilot study in 36 patients. Efficacy of riluzole in acute human SCI has not been established.

METHODS: This ongoing multi-center, international double-blinded phase III RCT will enroll 351 patients with acute C4—C8 SCI and ASIA Impairment Grade A, B or C randomized 1:1 to riluzole and placebo. Primary outcome is the change in ASIA Motor Score (AMS) between baseline and 180 days. Other outcomes include ASIA Upper and Lower Extremity MS; ASIA Sensory Score; ASIA grade; SCIM); SF-36v2; EQ-5D and GRASSP. Two-stage sequential adaptive trial statistical design has 90% power to detect 9 points difference in the ASIA Motor Score at

one-sided alpha = .025.

RESULTS: A matched cohort analysis performed in the Phase I study showed that riluzole treated cervical SCI patients experienced an additional 15.5 points in AMS recovery at 90 days post injury. Although the phase I study was underpowered to investigate efficacy the current phase II/III study is poised to definitive address this question. Subject enrollment for this trial began on October 1, 2013 in 11 international centers.

CONCLUSIONS: This is a Phase III study of riluzole in acute SCI.

III. Main theme

3 Clinical Trials

IV. Abstract Descriptors

- Use the following categories to list up to 3 abstract descriptors in descending order of priority.
- Example:

    1. 6e (robotics and exoskeletons)
    2. 4b (upper extremity function)
    3. 3d (physical therapy)

Descriptor 1	2a (Traumatic Injury)
Descriptor 2	4h (Other-ASIA Motor Score)
Descriptor 3	6b (Clinical Trials)

The following details are required in order for qualified health care professionals to obtain CME (continuing medical education) credits.

V. Documentation of FDA status for uses described

To obtain information regarding the clearance status of a device or pharmaceutical refer to the product labeling or call the FDA 1-800-638-2041 or visit the FDA internet site at http://www.fda.gov/cdrh/510khome.html

In my ‘work’ for this educational program or publication all pharmaceuticals and/or medical:

The FDA has cleared all pharmaceuticals and/or medical devices for the use described in this presentation. Please write “none” if it doesn´t apply as it cannot be left empty.

FDA clearence	No

The following pharmaceuticals and/or medical devices are being discussed for an off-label use.

Pharmaceuticals and/or medical devices	Sanofi-Aventis - Rilutek (Riluzole)

Academy policy provides that “off label” uses of a device or pharmaceutical may be described in the Academy’s CME activities so long as the “off-label” status of the device or pharmaceutical is also specifically disclosed (i.e. that the FDA has not approved labeling the device for the described purpose). Any device or pharmaceutical is being used “off label” if the described use is not set forth on the product’s approved label.

VI. Mandatory ASIA Financial Disclosure Statement

Please read the following statements and place a check in the box opposite the statement(s) which apply to you. If you **do not** have a financial interest or other relationship with a commercial company related directly or indirectly with the **Meeting** place a check in the first box. If you do have any financial interest or relationship to disclose please check the box and include the name of the commercial company. Your disclosure will be listed in the Final Program/Course Syllabus.

I (or a member of my immediate family) do not have a financial interest or other relationship with a commercial company or institution.	x

If you have any financial interest or other relationships please be sure to check all that apply below and include the company name:

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5. Do you or a member of your immediate family receive research or institutional support as a principal investigator from any pharmaceutical, biomaterial or orthopaedic device or equipment company, or supplier?

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6. ASIA Financial	Depuy Spine - Fellowship Support

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APPENDIX G

Financial Health

Comment on the financial health of the study. Was the study financially on track during this quarterly reporting period and cumulatively for completion as proposed within the period of performance? If not, describe the cause(s), whether this will have a short-term or long-term impact, the likelihood this can be overcome, and provide remediation strategy. Provide amount expended this quarter and cumulatively. State if there was any major equipment procured, sub-award implemented, and/or travel conducted.

COST ELEMENTS	**THIS QUARTER**	**CUMULATIVE**
Personnel		
Fringe Benefits		
Supplies	-	-
Equipment	-	-
Travel	-	-
Other Direct Costs		
Subtotal		
Indirect Costs		
Fee	-	-
Total		

Personnel Effort

Provide names of current staff along with their roles and percent effort of each on this project. Add additional rows if necessary to list the complete l team. If there is more than one project on this award, breakdown according to each project (one table per project).

Personnel	**Role**	**Percent Effort**
Robert Grossman MD	PI-Main	10
Elizabeth Toups RN	Project Manager	35
Tanisha Bernhardt	Project Assistant	50
Susan Howley	Admin	28
Peter Wilderotter	Admin	0.75
Melissa Burke	Admin	1.5
Vinithra Ramakrishnan	Admin	6.25
Michele Johnson, MD	PI	
Ann Saulino	Study Coordinator	50
Michael Fehlings, MD PhD, Charles Tator MD, PhD	Co-PIs	
Yuriy Petrenko	Study Coordinator	50
Christopher Shaffrey, MD	PI	
Judy Beenhakker	Study Coordinator	50
Susan Harkema, PhD, Maxwell Boayke, MD	Co-PIs	
Lori Clark	Study Coordinator	50
Bizhan Aarabi, MD	PI	
Christina Aldrich	Study Coordinator	50
James Guest, MD	PI	
Marina Dididze	Study Coordinator	50
James Harrop, MD	PI	
Jan Jaegar	Study Coordinator	50
Michael K. Rosner, MD	PI	
Vicki Miskovsky	Study Coordinator	50
Trey Mobley	Programmer	50.4
Heather Tolle	Data Manager	53.5
Diana Chow, PhD	PI	
Mahua Sarkar	Research Assistant	100
Joseph K. Hobbs, MD	PI	
Joseph Warren	Study Coordinator	50